National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 9 Highlights
Old Post Office, M09
1100 Pennsylvania Avenue
Washington, D.C.
March 10-12, 1998

INTRODUCTION

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 8 (December 8-10, 1997) were reviewed and approved as presented (Appendix A).

Dr. George Rusch (Chair) provided brief introductory remarks including the fact that the Standing Operating Procedures (SOP) were of high priority and that Dr. Falke would be presenting an overview of the SOP Working Group efforts later in the meeting. Dr. Morawetz (ICWUC) expressed concerns regarding the AEGL-3 values for carbon tetrachloride and that they may not be protective of alcoholics (Attachment 3). He also circulated a report pertaining to an accident involving the deaths of four workers following exposure to hydrogen cyanide that was generated by the interaction of muriatic acid and zinc cyanide during the cleaning of a vat (Attachment 4).

Dr. Paul Tobin (EPA-DFO) mentioned that plans were being made for a joint meeting with the National Academy of Sciences Committee on Toxicology for the June NAC/AEGL meeting.

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group

Dr. Ernest Falke (EPA) provided a summary of the SOP Working Group efforts. As previously stated by Dr. Garrett (Project Director), the SOP Working Group in addition to interpreting and expanding on the NAS guidelines (NAS, 1993), is documenting approaches used thus far in AEGL development. The SOP document currently addresses three major areas: (1) calculation of AEGL values, (2) format and content of technical support documents, and (3) development of information and data for technical support documents. Efforts pertaining to the first are on-going and include endpoints for AEGL levels as well as guidance for uncertainty factor and modifying factor application, time scaling, scientific rationale, policies for carcinogenic risk, use of NOAELs and LOAELs, and reconstruction modeling. This section also serves as a "living document" to capture approaches used by the NAC/AEGL in their development of AEGL values. The second area establishes format and consistency guidelines for the technical support documents, summary tables, rounding of AEGL values, and multiplication of uncertainty factors. The third major area provides guidance on assessing the quality of available data, and outlines the responsibilities and tasks of the chemical manager, chemical reviewer, and staff scientists developing draft AEGL values.

Federal Register Comments on Interim Draft AEGLs
Dr. Roger Garrett presented an overview of generic comments and issues from the Federal Register comment period (Attachment 5).

In response to the issue of establishing minimum data set guidelines, Dr. Roger Garrett stated that the NAC/AEGL relies on the NAS guidelines[1] (NAS, 1993) as a basis for AEGL development. It was also stated that the NAC/AEGL is captive to data that are available but that a 2/3 majority vote by the NAC/AEGL is required to AEGL values.

Regarding the use of NOAELs and LOAELs, Roger explained that AEGL levels are threshold effect levels. Additionally, attempts have been made and will continue to be made regarding the detailed and complete justification of uncertainty factors and default values in the development of AEGLs.

Some of the comments to the Federal Register notice pertained to definitions. A summary of these issues consistent with the annotation on page 2 of the public comments summary (Attachment 5) is presented below.

1. AEGL level definitions will be defined in more detail. Of special concern in this respect are chemicals that may not elicit AEGL-1 type effects.

2. For AEGL development, asthmatics are routinely considered a major subpopulation and not "hypersusceptible." They are not considered to be idiosyncratic responders.

3. The defining of protected populations was a recurring comment regarding the proposed AEGLs. A more definitive distinction between susceptible and hypersusceptible is required and will be addressed. Dr. Garrett also emphasized that children are routinely considered when developing AEGLs and that this effort is often guided by the presence of a pediatrician on the NAC/AEGL.

4. The fact that human infants <4 months old represent only 0.4% of the population was not a representative sensitive population to be included in AEGL development.

5. As previously noted, a more robust definition of susceptible vs hypersusceptible is considered appropriate. It was proposed that it may be useful to maintain an on-going list of examples pertaining to this issue and ultimately publish a solidification of NAC/AEGL and NAS thoughts on this issue.

6. Although it was originally planned to have a subcommittee of the NAC/AEGL address the issue of susceptible vs hypersusceptible populations, this effort is currently being addressed by the SOP Working Group.

7. Regarding comments that AEGL definitions are obscure and not reflective of customary definitions of health reference levels, it was emphasized that the AEGL definitions currently in place do, in fact, reflect the goals and endpoints that have been set by the NAC/AEGL and are consistent with NAS

[1] NAS (1993). Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Committee on Toxicology/National Research Council, National Academy Press, Washington, D.C.

guidelines. Furthermore, as previously stated, AEGLs are not "customary;" by definition, they represent effect/action levels.

8. The comment suggesting that AEGL-1 levels be protective of all potential adverse effects is not consistent with the definition.

Comments were also received regarding the application of uncertainty factors, the use of time scaling, the application of dosimetric adjustments, and the estimation of lethality by adjustment of LC_{50} values. Many of these were chemical-specific. However, general responses were in order for some of these issues. Uncertainty factor application will continue to be justified as thoroughly as possible. When appropriate data are available, time scaling has been based upon empirically derived and chemical specific information. The use of a default time scaling value and its inherent value or limitations is currently being addressed by the SOP Working Group. The application of dosimetric adjustments is also being revisited on a chemical-specific basis, and determination of toxicity thresholds (especially lethality thresholds) is constantly being examined by the NAC/AEGL and SOP Working Group.

Chemical-Specific Issues on Federal Register Proposed AEGLs

Aniline

No revisions or revisit by NAC/AEGL required.

Fluorine

No revisions or revisit by NAC/AEGL required.

Chlorine

In regard to the difference between the ERPG and AEGL values for chlorine, it was stated that the AEGL value places more emphasis on the response of the asthmatic. No revisions or revisit by NAC/AEGL required.

Nitric acid

No revisions or revisit by NAC/AEGL required.

Phosphine

No revisions or revisit by NAC/AEGL required.

Hydrazine

Concern regarding the use of a dosimetric conversion and its impact on the proposed AEGLs require revisiting. Additionally, the use of temporal extrapolation from a 24-hour exposure and the subsequent flat-line AEGL-1 values needs to be reassessed at the next NAC/AEGL meeting.

Methylhydrazine

The proposed AEGL values were originally calculated using an $n = 1$ for temporal scaling. More recently, an n value of 0.80 - 0.84 has been determined empirically from available data. AEGL values recalculated using a midpoint (n=0.82) of the empirically derived values of n resulted in elevated AEGL-2 and 3 values. Because the recalculation represented a more precise and complete use of the available data, the NAC/AEGL approved the revised values (YES:22; NO:1). No additional revisit required (Appendix B).

Original AEGL Values for Methylhydrazine (n=1.0)

AEGL-1	NA	NA	NA	NA
AEGL-2	2 ppm	1 ppm	0.2 ppm	0.1 ppm
AEGL-3	6 ppm	3 ppm	0.7 ppm	0.3 ppm
Revised AEGL Values for Methylhydrazine (n=0.82)				
AEGL-1	NA	NA	NA	NA
AEGL-2	5.2 ppm	2.2 ppm	0.4 ppm	0.18 ppm
AEGL-3	25 ppm	11 ppm	2 ppm	0.86 ppm

1,1-Dimethylhydrazine & 1,2-Dimethylhydrazine

A suggestion was made and approved to include cancer risks of 10^{-5} and 10^{-6} in the carcinogenic risk calculation Appendix. Additionally, a description regarding use of the noncancer endpoint for AEGL development was made (this verbiage is already in the technical support document). No additional revisit required.

1,2-Dichloroethylene

No revisions or revisit by the NAC/AEGL required.

Ethylene oxide

There was concern was regarding the use of data from a dominant lethal study for development of AEGL-2. It was suggested that Judy Strickland EPA-RTP) be invited to address the NAC/AEGL and that ethylene oxide be revisited at the next NAC/AEGL meeting.

Arsine

No revisions or revisit by the NAC/AEGL required.

Review of Proposed AEGLs to be Submitted to Federal Register for Public Comment

A reaffirmation of the second set of proposed draft AEGLs for 11 chemical substances was conducted by the NAC/AEGL. The technical support documents were distributed to NAC/AEGL members for review relative to currently available SOPs. The respective chemical managers for these chemicals provided comments on the current status of these chemicals.

Allyl alcohol	-	no additional comments
Allyl amine	-	no further comments
Ammonia	-	no comments
Boron trichloride	-	no additional comments
Chlorine trifluoride	-	current document and proposed draft AEGLs are consistent with NAC/AEGL procedures and approaches
Diborane	-	current document and proposed draft AEGLs reflect NAC/AEGL deliberations
Ethylenimine	-	current document and proposed draft AEGLs reflect NAC/AEGL deliberations
Hydrogen chloride	-	only editorial adjustments required

Methyl mercaptan	-	rationale for AEGL-1 incorporated as required
2,4 -Toluene diisocyanate	-	one minor comment to be incorporated; no substantial changes
2,6 -Toluene diisocyanate		required for the toluene diisocyanates

General Interest Items

- George Rusch reported that both the German MAK Commission and the Threshold Limit Value Committee of the American Conference of Governmental Industrial Hygienist consider irritation a threshold phenomena independent of exposure duration and that this is consistent with the NAC/AEGL position.
- John Hinz stated that there is a symposium on jet fuels scheduled at Brooks AFB in April, and that the NAC/AEGL deliberations on jet fuels AEGLs be postponed until at least Dec. 1998.
- The response to Federal Register comments should be from the NAC/AEGL proper and not from an individual.

AEGL PRIORITY CHEMICALS

Bromine, CAS No. 7726-95-6

Chemical Manager: Dr. Zarena Post, TX Nat. Resource Conserv. Comm.
Author: Dr. Sylvia Talmage, ORNL

In Dr. Post's absence, Dr. Larry Gephart (Exxon Biomedical) served as chemical manager for bromine. An overview of the limited data was provided by Dr. Sylvia Talmage (Attachment 6). Sylvia noted that the data was difficult to interpret with respect to application to AEGL development. Following a brief discussion, it was the consensus of the NAC/AEGL that a request be made to industry to conduct an RD_{50} (Respiratory Depression) study and also to obtain an LC_{50} in a species other than the mouse rather than proceeding with AEGL development. The development of AEGL values for bromine will be tabled pending results of the research inquiry. An assessment of the research feasibility or possibility of obtaining more data will be presented at the June meeting, at which time a decision will be made whether or not to proceed with the limited available data.

Action Item: Larry Gephart and Steve Barbee were asked to check into industrial sponsorship regarding research needs consistent with developing AEGL values. A status report was requested for the next NAC/AEGL meeting.

Nitric oxide, CAS No.10102-43-9

Chemical Manager: Dr. Loren Koller, Oregon State Univ.
Author: Dr. Carol Forsyth, ORNL

Dr. Carol Forsyth reviewed the limited data for nitric oxide (Attachment 7) explaining that additional data consistent with AEGL development needs were presented at the recent Society of Toxicology meeting. These data have been requested. Data were limited to developing only AEGL-1 values; 80 ppm for all time points based upon methemoglobin formation and no uncertainty factors. Discussion proceeded and revolved around the conversion of nitric oxide to nitrogen dioxide under ambient conditions, and the fact that off-site

populations may be exposed to that latter. Debate ensued regarding the relevance of NO vs NO_2 AEGLs and the need for AEGLs for NO, NO_2, or both. Concern was also expressed regarding the validity of 4- and 8-hour values for NO. Dr. Borak stated that the methemoglobin formation is a marker of exposure and that individuals exposed during accidental releases would likely experience NO_2-induced respiratory tract irritation prior to health-impairing methemoglobin formation. It was the consensus of the NAC that AEGLs be developed for NO but that they be held in abeyance until data on NO_2 can be examined. AEGL values for NO_2 will be derived for comparison to NO. Both chemicals will be then addressed.

Action Item: Paul Tobin will check with NASA regarding potential for N_2O_4 AEGL development.

Chloromethyl methyl ether, CAS No. 107-30-2

Chemical Manager: Dr. Ernest Falke, EPA
Author: Dr. Sylvia Milanez, ORNL

Dr. Falke presented a summary of the major issue regarding chloromethyl methyl ether (CMME) and Dr. Sylvia Milanez provided an overview (Attachment 8) of the available data and development of the AEGLs. A major point of discussion focused on the carcinogenic potential of this chemical, specifically an analog that is virtually always present as a contaminant. A 10^{-4} cancer risk was calculated for CMME. Discussion ensued regarding the selection of the cancer risk level of concern. Generally, the majority of NAC members believed that the 10^{-4} risk was appropriate for a once-in-a-lifetime exposure and to avoid creating an atmosphere of anxiety regarding potential cancer risk in light of deficient data. A poll of the NAC indicated that, based upon available data, it was more appropriate to develop AEGL values based upon noncancer toxicity. A motion was made by Dr. George Rodgers (seconded by Dr. Loren Koller) to accept the draft AEGL values as presented in the TSD. The motion carried (YES:23; NO:0; ABSTAIN:0 for AEGL-1 and AEGL-3; YES:21; NO:2; ABSTAIN:0 for AEGL-2) (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR CHLOROMETHYL METHYL ETHER

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	ND	ND	ND	ND	No studies available
AEGL-2	0.12 ppm (0.38 mg/m^3)	0.082 ppm (0.27 mg/m^3)	0.041 ppm (0.13 mg/m^3)	0.029 ppm (0.095 mg/m^3)	tracheal/bronchial squamous metaplasia; regenerative hyperplasia
AEGL-3	1.8 ppm (6.1 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.65 ppm (2.1 mg/m^3)	0.46 ppm (1.5 mg/m^3)	7-hr LC_{01} in rats

ND: no data

Action item: As a result of the discussion regarding cancer risk for CMME, it was decided that the subject be addressed in a short issue paper to be attached as an appendix to the technical support document. Dr. Richard Thomas agreed to prepare a brief issue paper as an initial effort regarding the application of carcinogenic risk to AEGL development.

Dimethyldichlorosilane, CAS No. 75-78-5
Methyltrichlorosilane, CAS No. 75-79-6

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL

Dr. Cheryl Bast reviewed the data for these chemicals and provided new 1-hour rat lethality data for dimethyldichlorosilane received from Dow Corning Corporation (Attachment 9). Chemical-specific data were unavailable for AEGL-1 and, therefore, the values were developed by analogy to HCl (degradation of dimethyldichlorosilane will yield 2 moles of HCl). Dr. Bast stated that an industry representative explained that although some anecdotal information suggest that the toxicity of some chlorosilanes may differ from that of HCl, newer data suggest that the toxicity of commercial chlorosilanes is similar to that of HCl. Assuming maximum degradation to HCl and equivalent sensitivity of exercising asthmatics (the endpoint used for the HCl AEGL-1 values), the AEGL-1 for dimethyldichlorosilane for all time points was proposed as one half the HCl values (0.9 ppm). The motion to accept these values (made by Dr. David Belluck and seconded by Dr. Thomas Hornshaw) passed unanimously (YES:17; NO:0; ABSTAIN:0). The AEGL-2 values (26 ppm, 13 ppm, 3.3 ppm, and 1.6 ppm for the 30 min. 1, 4, and 8-hour time points) were based upon a 1-hr exposure concentration of 1,309 ppm, a total uncertainty of 100 (10 for interspecies variability, 3 for individual variability, and a data base modifying factor of 3), and $n = 1$. A motion made by Dr. George Rodgers and seconded by Dr. David Belluck passed unanimously (YES:17; NO: 0; ABSTAIN:0). The AEGL-3 values (106 ppm, 53 ppm, 13 ppm, 6.6 ppm for the 30-min, 1, 4, and 8-hour periods) were based upon an estimated lethality threshold and incorporated an uncertainty factor of 30, and $n = 1$. A motion by Dr. Hornshaw (seconded by Dr. Belluck) to accept these values passed unanimously (YES:17; NO:0; ABSTAIN:0) (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	Two-fold reduction of the HCl AEGL-1 which was based upon no effect level in exercising asthmatics
AEGL-2	26 ppm (140 mg/m^3)	13 ppm (69 mg/m^3)	3.3 ppm (18 mg/m^3)	1.6 ppm (8.5 mg/m^3)	Corneal opacities; grey spots on lungs of rats (1309 ppm, 1 hr)
AEGL-3	106 ppm (562 mg/m^3)	53 ppm (281 mg/m^3)	13 ppm (69 mg/m^3)	6.6 ppm (35 mg/m^3)	Lethality threshold in rats (1590 ppm, 1 hr)

Dr. Bast presented the data and draft AEGL derivations for methyltrichlorosilane (Attachment 10). Similar to the dimethydichlorosilane, the AEGL-1 was based on analogy to the HCl AEGL-1 and the degradation of the methyltrichlorosilane to 3 moles of HCl. A motion to accept 0.6 ppm as the AEGL-1 for all time points was made by Dr. Hornshaw, seconded by Dr. Steven Barbee, and passed unanimously (YES:17; NO:0; ABSTAIN:0). The AEGL-2 values were based upon ocular opacities in rats exposed for 1 hour to 622 ppm. Using a total uncertainty factor of 30, and n=1, the resulting AEGL-2 values of 12, 6.2, 1.6, and 0.78 ppm

were accepted unanimously (motion made by Dr. Rodgers and seconded by Dr. Niemeier); (vote: YES:17; NO:0; ABSTAIN:0). Following discussions regarding the value of *n* for temporal extrapolation and uncertainty factor application and a by Dr. Rodgers (seconded by Dr. Barbee), the AEGL-3 values of 56, 28, 7, and 3.5 ppm (*n*=1, UF = 30) were unanimously accepted (YES:17; NO:0; ABSTAIN:0) (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR METHYLTRICHLOROSILANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	Three-fold reduction of the HCl AEGL-1 which was based upon a no-effect level in exercising asthmatics
AEGL-2	12 ppm (73 mg/m^3)	6.2 ppm (38 mg/m^3)	1.6 ppm (9.8 mg/m^3)	0.78 ppm (4.8 mg/m^3)	Ocular opacities in rats exposed for 1 hour to 622 ppm
AEGL-3	56 ppm 342 mg/m^3)	28 ppm (171 mg/m^3)	7 ppm (43 mg/m^3)	3.5 ppm (21 mg/m^3)	Lethality threshold in rats (1-hr) of 844 ppm

Epichlorohydrin, CAS No. 106-89-8

Chemical Manager: Dr. Richard Thomas, ICEH
Author: Dr. Kowetha Davidson, ORNL

Dr. Richard Thomas presented a brief introduction (Attachment 11) followed by an overview of the data and development of the draft AEGLs by Dr. Davidson (Attachment 12). Lynn Harris of the Technical Affairs Office, Society of Plastics Industry, Inc. was also in attendance as an observer. Concerns were discussed regarding the AEGL-1 uncertainty factor application and variability in the irritation response observed for epichlorohydrin. Although the reported odor threshold for epichlorohydrin ranges from 0.08 to 20 ppm (recognition at 20 ppm) and irritation is known to occur at >10 ppm, it was the consensus of the NAC that 5 ppm be considered for all AEGL-1 time points and that this would represent a protective estimate of the irritation threshold. The NAC noted that this may be a subthreshold for odor perception. A motion was made by Larry Gephart (seconded by Dr. Loren Koller) to accept the 5 ppm values. The motion carried (YES:21; NO:1; ABSTAIN:0). For the AEGL-3, initial discussions focused on the uncertainty factor application and whether or not the 8-hour AEGL-3 value should be developed independently of the other time frames (the 8-hr values [19 ppm] developed from the key studies would be inconsistent with the definition of AEGL-3). The 8-hr AEGL-3 was developed from a study showing that long-term exposures to 30 ppm did not result in shortening of life. A motion was made (Dr. Borak; seconded by Dr. Belluck) and carried to accept AEGL-3 values of 160 ppm, 72 ppm, and 43 ppm for the 30-min, 1-hour, and 4-hour time points (YES:17; NO:2; ABSTAIN:2). Following discussions on developing the 8-hour AEGL-3 value using data from a long-term study, the 8-hour AEGL of 30 ppm was considered to be protective of life-threatening effects following an 8-hour exposure and was accepted (motion by Dr. Borak, seconded by Dr. Belluck; YES:14; NO:1; ABSTAIN:5). For the development of AEGL-2 values, there were discussions regarding identification of an appropriate endpoint. There was extensive discussion on the draft proposed AEGL-2 values from the TSD which were based upon irritation (burning eyes). Although AEGL values for irritation are usually flat-lined, this was not considered desirable for the AEGL-2. Some committee members also expressed concerns about using this endpoint for AEGL-2 values. Ultimately, it was the consensus of the NAC that the AEGL-2 values

be derived by a 3-fold reduction in the AEGL-3 value and that this would be protective of pulmonary edema observed in animal lethality studies. A motion to accept this rationale and consequent values (53 ppm, 24, pp, 16, ppm and 10 ppm) was made by Dr. George Rodgers and seconded by Dr. Niemeier. The motion passed (YES:16; NO:2; ABSTAIN:1) (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR EPICHLOROHYDRIN					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	5 ppm (18.9 mg/m^3)	5 ppm (18.9 mg/m^3)	5 ppm (18.9 mg/m^3)	5 ppm (18.9 mg/m^3)	Odor irritation threshold
AEGL-2	53 ppm (200.3 mg/m^3)	24 ppm (90.7 mg/m^3)	16 ppm (60.5 mg/m^3)	10 ppm (37.8 mg/m^3)	3-fold reduction in AEGL-3 values to protect against pulmonary edema
AEGL-3	160 ppm (604.8 mg/m^3)	72 ppm (272.2 mg/m^3)	43 ppm (162.5 mg/m^3)	30 ppm (113.4 mg/m^3)	Lethality threshold

Nickel carbonyl, CAS No. 13463-39-3

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Robert Young, ORNL

Dr. Blackman opened the presentation by discussing unique physicochemical properties (e.g., degradation properties, dissociation rates, etc.) of nickel carbonyl, especially those that would impact on exposures resulting from accidental releases of the chemical (Attachment 13). Dr. Young presented an overview of the data, emphasized that data were limited to lethality and developmental studies (Attachment 14). He explained that application of a full complement of uncertainty factors (i.e, 10 x 10) as used in the draft AEGLs may be inappropriate due to the fact that LC_{50} data for four species appeared to suggest that larger species were less sensitive. No data were available that were consistent with AEGL-1 endpoints. Furthermore, the toxicity and latency period associated with nickel carbonyl exposures (human case reports often indicated severe or lethal toxic responses hours to days after an initial exposure) are of concern. Two developmental toxicity studies were available from two studies (rat and hamster) that could possibly be used as drivers for AEGL-2 values but would be relationally inconsistent with AEGL-3 values derived using the full complement of uncertainty factors. Following a brief discussion, it was the consensus of the NAC that the AEGL-3 be derived using an estimate of the lethality threshold (LC_{01} of 3.17 ppm) in the most sensitive species (mouse), a total uncertainty factor of 10 (3 for interspecies variability and 3 for intraspecies variability), and default of $n = 2$. The motion to accept the AEGL-3 values of 0.32 ppm, 0.22 ppm, 0.11 ppm, and 0.08 ppm (made by Dr. McClanahan; seconded by Larry Gephart) carried (YES:13; NO:2; ABSTAIN:2) (Appendix G). Due to the lack of additional time, further deliberations and discussions regarding the development of an AEGL-2 based upon the developmental toxicity data in animals, and the status of AEGL-1 were tabled until the next meeting.

SUMMARY OF PROPOSED AEGL VALUES FOR NICKEL CARBONYL					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint

AEGL-1	-	-	-	-	
AEGL-2	-	-	-	-	
AEGL-3	0.32 ppm	0.22 ppm	0.11 ppm	0.08 ppm	Estimated lethality threshold (LC_{01} of 3.17 ppm) in mice, UF=10; *n*=2

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

June 8-10, 1998, Washington, D.C.; possible joint meeting the COT
September 14-16, 1998, Oak Ridge, TN

Prepared by: Drs. Robert Young and P.Y. Lu, Oak Ridge National Laboratory, Oak Ridge, TN

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC Meeting No. 9 Agenda
2. NAC Meeting No. 9 Attendee List
3. Information provided by John Morawetz
4. Information provided by John Morawetz
5. Public comments for proposed draft AEGL values
6. Data analysis of Bromine - Sylvia Talmage
7. Data analysis of Nitric oxide - Carol Forsyth
8. Data analysis of Chloromethyl methyl ether - Sylvia Milanez
9. Data analysis of Dimethyldichlorosilane - Cheryl Bast
10. Data analysis of Methyltrichlorosilane - Cheryl Bast
11. Overview of Epichlorohydrin - Richard Thomas
12. Data analysis of Epichlorohydrin - Kowetha Davidson
13. Overview of Nickel carbonyl - Kyle Blackman
14. Data analysis of Nickel carbonyl - Robert Young

LIST OF APPENDICES

A. Approved NAC-8 Meeting Highlights
B. Ballot for Methylhydrazine
C. Ballot for Chloromethyl methylether
D. Ballot for Dichlorodimethylsilane
E. Ballot for Methyl trichlorosilene
F. Ballot for Epichlorohydrin
G. Ballot for Nickel carbonyl

Attachment 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Old Post Office, M09
1100 Pennsylvania Avenue, N. W.
Washington, D.C. 20506

NAC-9

AGENDA

Tuesday, March 10, 1998

10:00 - 10:15	AM	Introductory remarks and approval of NAC/AEGL-8 highlights (George Rusch, Roger Garrett and Paul Tobin)
10:15 - 12:15	PM	Bromine (Zarena Post/Sylvia Talmage)
12:15 - 1:15		**Lunch**
1:15 - 3:15		Nitric oxide (Loren Koller/Carol Forsyth)
3:15 - 3:30		**Break**
3:30 - 5:30		Chloromethyl methyl ether (Ernie Falke/Sylvia Milanez)

Wednesday, March 11, 1998

8:30 - 9:30	AM	SOP Workgroup report (Ernie Falke)
9:30 - 10:30		Status review of chemicals for Interim AEGLs
10:30 - 10:45		**Break**
10:45 - 12:00	PM	Status review of chemicals for Proposed AEGLs
12:00 - 1:00		**Lunch**
1:00 - 2:30		Dimethyldichlorosilane & Methyltrichlorosilane (Ernie Falke/Cheryl Bast)
2:30 - 2:45		**Break**
2:45 - 4:45		Epichlorohydrin (Richard Thomas/Kowetha Davidson)
4:45 - 5:30		Nickel carbonyl (Kyle Blackman/Bob Young)

Thursday, March 12, 1998

8:30 - 9:30	AM	Nickel carbonyl (continued)
9:30 - 11:30		Acrolein (Bob Snyder/Cheryl Bast)
11:30 - 12:30	PM	Administrative issues
12:30		Adjournment

Attachment 2

NAC/AEGL-9

3/10-12/98

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ICWUC CENTER FOR WORKER HEALTH AND SAFETY EDUCATION

Training Programs for Emergency Response, Hazardous Waste and Nuclear Workers

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Attachment 3

March 6, 1998

Paul Tobin
US EPA, MS 7406
401 M Street, SW
Washington, D.C. 20460

Dear Paul:

I would like to bring to your attention a study that was referenced in the determination of the AEGL 3 level for Carbon Tetrachloride, the Norwood et. al. (1950) report mentioned in section 2.1 on Acute Lethality. It summarizes the case of a worker who died after working with carbon tetrachloride for 15 minutes. The AEGL document states in summary that "an exposure reconstruction provided an estimate of the exposure concentration (250 ppm)." The Oak Ridge National Labs provided me with the actual study (pertinent pages enclosed). It states "The conditions under which this man was exposed were duplicated to the best of our ability, and the measured concentration was 250 parts of carbon tetrachloride per million parts of air."

Table 2 states that this exposure was "estimated". Although I believe reasonable estimates of exposure should be considered, this study "duplicated to the best of our ability" the exposure level. Without any further information to determine if this reconstruction was high or low, we should accept it as written.

This study is crucial in the setting of an exposure level that could result in death for alcoholic individuals. Section 2.1 states "It is curious that two individuals continued the floor cleaning and were subject to the same exposure conditions (... and) reported very mild headaches and some dizziness". Rather than "curious", this is consistent with the significantly greater effects for alcoholics, a significant percentage of the population.

The committee raised the initial proposal of 68 ppm for a 30 minute AEGL-3 to 230 ppm. This worker died after exposure to 250 ppm for 15 minutes, twice the time period we are determining. Relying on laboratory rat studies may be protective of most adults but there is significant evidence that it is not protective of alcoholics.

I urge the committee to reconsider this determination.

Sincerely,

John S. Morawetz

c: Frank D. Martino
Michael Sprinker
Peg Seminario
AEGL Committee

AMA. Ind. Hyg. Occup. Med. 1:90-100 1950

CARBON TETRACHLORIDE POISONING

More Regulation, More Education Needed

W. D. NORWOOD, M.D.
P. A. FUQUA, M.D.
AND
B. C. SCUDDER, M.D.
RICHLAND, WASH.

IT IS REGRETTABLE that noninflammable carbon tetrachloride, CCl_4, an excellent organic solvent, is also toxic and takes a heavy toll in lives each year.

The present article will summarize the need for better regulation of the distribution, sale and use of this toxic agent as proved by sad experience on a large construction project and in the city from which these construction activities were directed. Fairhall,[1] of the United States Public Health Service, stated that the carbon tetrachloride produced in 1946 totaled 145,766,000 pounds. The major consumption is as follows: About 56.5 per cent is used in the manufacture of dichlorodifluoromethane (freon 12®), which is largely used as a refrigerant, and more recently as an insecticide (DDT) dispersant. About 11.6 per cent is used in fire extinguishers, 8 per cent in commercial dry cleaning and 3.5 per cent in fumigation of grain. Carbon tetrachloride finds extensive but diminishing use in the degreasing of oily machine parts and electrical equipment. It is also used in the extraction of oils from press cakes and oil-bearing seeds and in the degreasing of hides, bones and garbage.

A high percentage of American homes always have a can of cleaning fluid for removing grease spots from clothing or for other purposes. The label rarely states that the fluid contains carbon tetrachloride in a high concentration, nor is any mention made of the toxic nature of the fluid. It is worth repeating [2] that:

> Toxic reactions to carbon tetrachloride may result from a single brief exposure to a high concentration of the vapor, from prolonged or repeated exposure to a moderately high concentration, or from regular daily exposure to low concentrations in excess of accepted safe limits; from repeated contact of the skin with the liquid, or from ingestion of the liquid.

From the Medical Division, Hanford Works, Nucleonics Department, General Electric Company.

1. Fairhall, L. T.: Carbon Tetrachloride, Indust. Hyg. Newsletter **8**:7, 1948.
2. The Recognition and Treatment of Carbon Tetrachloride Poisoning, Council on Industrial Health, J.A.M.A. **132**:786 (Nov. 30) 1946.

During the last twelve months, in two communities with a combined population of thirty thousand people, we have observed 2 fatalities, 1 near fatality and 4 other cases requiring hospitalization of the patient, due to carbon tetrachloride poisoning. In addition, 51 industrial cases of probable mild toxicity were studied. None of the 3 very severe cases were due to exposure in industrial operations. This checks with the statements of others [3] that in most instances fatal poisoning has occurred in isolated or individual use of carbon tetrachloride as contrasted to its use in industry.

REPORT OF CASES

CASE 1.—A 22 year old white man, a janitor, was admitted to Kadlec Hospital (medical service of Dr. P. E. Kendall) on March 31, 1948 because of generalized aches and pains, nausea and vomiting of six hours' duration.

Past History.—He had been hospitalized in 1947 for influenza. Since his discharge from the Navy, in 1946, he had been a heavy drinker of alcoholic liquors, consuming "at least a fifth each week end."

Present Illness.—The patient stated that he felt well until twenty-four hours prior to admission, when he suffered from headache and dizziness after using carbon tetrachloride to clean stains from an office floor. Fellow workmen reported that he had not worked the previous day and did not "feel well" on the day he reported for work. He used a mop in a 3 gallon (13.5 liter) bucket about one-third full of liquid. After mopping the floor for about fifteen minutes, he was bothered with headache and dizziness and was given other work. His two associates continued the mopping under the same conditions for a total of about four hours, so it may be reasonably assumed that their exposure was many times greater; yet they had only very mild headache and dizziness, and did not consider stopping work. This discomfort cleared as soon as they stopped mopping. The work was done on the night shift and without the knowledge or the sanction of the supervisor. However, the liquid was readily available, and the workmen had not been warned of its toxicity as they were not expected to use it. The patient used approximately a half gallon (2.5 liters) of carbon tetrachloride in cleaning the floor of a room 15 by 16 by 8 feet (4.5 by 5 by 2.5 meters). It was well ventilated by a vent delivering 144 cubic feet of air per minute, with appropriate exhaust through an open door into the building proper, where a slight negative gradient was maintained to the exhaust fan. This would give about one air change in the room during the fifteen minutes of exposure. The conditions under which this man was exposed were duplicated to the best of our ability, and the measured concentration was 250 parts of carbon tetrachloride per million parts of air.

Physical Findings.—This fairly well developed young man did not appear to be critically ill. The mucous membranes of nose and throat were injected. Some submaxillary nodes were slightly enlarged and tender. The chest findings were normal. There was some increased tension of the muscles of the right upper and

3. Abbott, G. A., and Miller, M. J.: Carbon Tetrachloride Poisoning: A Report on Ten Cases at the United States Marine Hospital, Seattle, Wash., since 1937, Pub. Health Rep. **63**:50 (Dec. 10) 1948. Martin, W. B.; Dyke, L. H.; Coddington, F. L., and Snell, A. M.: Carbon Tetrachloride Poisoning: A Report of One Case with Necropsy and One Non-Fatal Case with Clinical Laboratory Studies, Ann. Int. Med. **25**:488 (Sept.) 1946.

lower quadrants of the abdomen, and the liver was palpable 4 cm. below the costal border. The temperature was 99.4 F.; the pulse rate, 88 and regular; the respiratory rate, 20, and the blood pressure, 120 systolic and 70 diastolic.

Laboratory Findings.—The hemoglobin was 14.5 Gm. in 100 cc.; the red cell count was 4,700,000; the white cell count, 16,150, with 95 per cent polymorphonuclear leukocytes and 5 per cent lymphocytes. The Kahn test was negative. The first voided urine specimen was missed. Only 250 cc. of urine was obtained by voiding and by catheterization during the six hospital days. The specimen obtained by catheter on the fourth day showed a specific gravity of 1.019, an acid reaction, a 2 plus reaction for albumin, a 1 plus reaction for sugar and 1 to 2 white blood cells per high power field. Urine obtained by catheter on the fifth hospital day showed a specific gravity of 1.012, an alkaline reaction, a 4 plus reaction for albumin, 20 to 25 white blood cells and 0 to 2 red blood cells per high power field, and 0 to 1 fine granular casts and 0 to 2 coarse granular casts per high power field. On the fifth day of hospitalization the blood revealed urea nitrogen to be 68 mg. in 100 cc.; carbon dioxide–combining power 42 volumes per cent; the icterus index, 14 units; the blood chlorides, 320 mg. in 100 cc. On the sixth day the blood urea nitrogen was 102 mg. in 100 cc., the carbon dioxide–combining power 42 volumes per cent and blood chlorides 405 mg. in 100 cc.

A preplacement roentgenogram of the chest, taken in August 1947, was not remarkable, and since the patient had no symptom referable to the chest, a roentgenogram of the chest was not made on admission to the hospital.

With oliguria, changing to anuria, azotemia, increasing hypertension (to 150 systolic, 110 diastolic) and edema of the face and eyelids, a diagnosis of acute renal insufficiency became obvious. Intravenous dextrose was administered at first.[4] As soon as a diagnosis of acute renal insufficiency was made, the total intake of fluid was limited to equal the calculated loss. Acidosis was regulated with sodium lactate. The blood chlorides were carefully followed. Oxygen was administered for early cyanosis and impending pulmonary edema. The patient became progressively worse; pulmonary edema developed and death occurred on the sixth hospital day.

Autopsy.—Gross Observations: Mild icterus of the scleras was observed, though the skin was clear. Numerous petechial conjunctival hemorrhages were present. The nose and the mouth were filled with a frothy bloody exudate. Bloody fluid was present in both pleural cavities. The lungs were engorged with blood. The pericardial cavity was clear, while the peritoneal cavity contained about 300 cc. of clear straw-colored fluid. The liver was enlarged to 6 cm. below the costal margin and weighed 2,050 Gm. The cut section showed marked accentuation of the lobular markings.

Chemical examination of kidney and liver for carbon tetrachloride failed to reveal its presence.

Microscopic Observations: Heart, lungs, bronchi, liver, spleen, adrenal glands, kidney and esophagus were examined histologically. Sections of liver and kidney were sent to two recognized pathologists.

The first report (T. B. Mallory, pathologist, Massachusetts General Hospital, Boston) was as follows: "The liver shows sharp central necrosis without as yet significant evidence of regeneration. The kidney shows typical lower nephron nephrosis, with pigment casts, degeneration of the ascending limbs of Henle's loop, interstitial inflammation of the corticomedullary junction and foci of venous

4. Smetana, H.: Nephrosis Due to Carbon Tetrachloride. Arch. Int. Med. **63**:760 (April) 1939. Council on Industrial Health.[2]

thrombosis. The findings are entirely characteristic of carbon tetrachloride poisoning, though not specific, as the condition can be produced by other toxic agents, such as mushroom poisoning. . . . the synergic effect of alcoholism in carbon tetrachloride injury is well established both experimentally and from clinical experience. It is very probable that it played a contributory role in this case."

The second report (E. T. Bell, pathologist, University of Minnesota Medical School, Minneapolis) was as follows: "The liver shows severe central necrosis of the lobules, and the kidneys show interstitial edema and hydropic degeneration of the tubules. These findings are consistent with carbon tetrachloride poisoning. In fact, when taken with the clinical history, the diagnosis of carbon tetrachloride poisoning is practically certain. 'Alcoholics' or persons who are under the influence of alcohol during the exposure to carbon tetrachloride usually sustain much more severe poisoning than persons not using alcohol. This probably explains the fact that the other men were only slightly affected."

CASE 2.—A 36 year old white man was admitted to Kadlec Hospital (medical service of Dr. P. E. Kendall; treatment, Dr. C. J. McGee), Dec. 12, 1948, complaining of epigastric distress, numbness of the upper extremities and vomiting.

Past History.—He had been a heavy drinker of alcoholic beverages since the age of 21, consuming 2 or 3 quarts (2 or 3.5 liters) of liquor each week. The results of a recent preplacement physical examination were essentially normal.

Present Illness.—He was well until twelve hours before admission, when epigastric distress developed, associated with pain in the back, numbness of the arms and hands, and vomiting, which continued at frequent intervals.

Physical Findings.—There was marked tenderness in the hypochondrium with some rigidity.

Laboratory Findings.—On admission the urine showed a reaction for albumin (3 plus), a specific gravity of 1.017, an acid reaction and absence of sugar. Microscopic examination of the urine showed many granular casts with occasional white and red blood corpuscles. The blood cell count was normal except for slight leukocytosis.

Course.—During the first day of hospitalization it was necessary to consider the possibility of an acute surgical abdominal condition, a peptic ulcer with slow leakage at a perforation. This was ruled out, and on the third day an intravenous pyelogram showed no visible dye anywhere in the urinary tract, even in the bladder, up to a maximum of an hour and fifteen minutes. By this time, acidosis was evident, with carbon dioxide–combining power of 36 volumes per cent and blood urea nitrogen 86.7 mg. in 100 cc. A probable diagnosis of acute renal insufficiency was made.

On the fourth hospital day the wife, on cross questioning, revealed that thirty-six hours before admission the patient had put out a fire by using a carbon tetrachloride fire extinguisher in a nearly closed small space and that the fumes were bad. The fire had occurred in the insulation around water pipes under the sink.

The urinary output continued low, with acidosis and high blood urea nitrogen. A diagnosis of lower nephron nephrosis due to carbon tetrachloride poisoning was made.

Consideration was given to sending the patient to a center where he could be treated with an artificial kidney, or to doing peritoneal or intestinal lavage, but it was felt that he would fare as well under the revised conservative treatment.

Extensive chemical study of the blood was done almost daily to follow the course of acidosis, chlorides, calcium and other factors, in order that appropriate treatment might be given. The fluid output was religiously watched and the

amount of the daily administered fluids limited to the calculated fluid output. This was about 1,000 cc. during the acute phase, the daily urinary output ranging from 100 to 300 cc. It was felt that this patient's life was saved by limiting the intake of fluids, thereby lessening the likelihood that the tissues would be flooded, especially the lungs. The patient left the hospital on Jan. 17, 1949, the kidneys having resumed fairly normal function by January 9, seventeen days after the initial damage.

A number of fatalities from phosgene poisoning have resulted when carbon tetrachloride fire extinguishers were used in confined places, such as mines or inside of buildings.[5]

The findings in these 2 cases are typical of the syndrome which is now known to develop secondarily to any of a wide variety of conditions involving shock and destruction of tissue or blood.[6] Such conditions include transfusion reactions, burns, crushing injuries, fulminating infections, sulfonamide toxicities and various chemical and vegetable poisonings. The renal changes involve the lower segments of the nephrons—with necrosis and focal degeneration of the tubules of Henle and of the distal convoluted tubules. Lucké[7] has called the syndrome "lower nephron nephrosis." Death is frequent in cases of this condition and usually occurs within ten days. The primary cause of the renal lesions is now generally thought to be cortical ischemia.[8] These studies indicate that regeneration of the tubules begins within about four days and that most of the damaged lining is repaired within ten days. Therapy is based on the fact that if the patient can be kept alive through the self-limited period of oliguria and/or anuria, there will probably be little, if any, permanent damage to the kidneys.

It is important to realize that during the period of shock or low blood pressure, intravenous injections of fluids, blood transfusions, administration of oxygen and the other measures usually employed are indicated.[8] However, as soon as renal insufficiency is evident, the total fluid intake should be limited to the daily calculated loss. Frequent laboratory examinations are essential to guide the administration of sodium lactate or bicarbonate in the treatment of acidosis, of calcium

5. Technical Paper 248, United States Department of the Interior, Bureau of Mines, 1921; cited by Henderson, Y., and Haggard, H. W.: Noxious Gases and the Principles of Respiration Influencing Their Action, American Chemical Society Monograph Series, New York, The Chemical Catalog Company, 1927, p. 136.

6. Mallory, T. B.: Hemoglobinuric Nephrosis in Traumatic Shock, Am. J. Clin. Path. **17**:427 (June) 1947. Thorn G. W.: Treatment of Renal Insufficiency, J. Urol. **59**:119 (Feb.) 1948.

7. Lucké, B.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons). Mil. Surgeon **99**:371 (Nov.) 1946.

8. Snyder, H. E., and Culbertson, J. W.: Pigment Nephropathy in Battle Casualties, Arch. Surg. **56**:651 (May) 1948. Van Slyke, D. D.: The Effect of Shock on the Kidney, Ann. Int. Med. **28**:701 (April) 1948.

gluconate in the treatment or the prevention of tetany, and of salt and fluid in the control of edema. When in recovery diuresis occurs, therapy is concerned with replacement of the urinary losses of sodium, water and potassium. If these measures appear to be failing, two others may be tried if facilities are available. These are (1) interrupting the splanchnic nerve supply to the kidneys by renal decapsulation or by splanchnic block[9]; (2) providing a temporary substitute for the glomeruli that will permit removing toxic end products of metabolism from the blood until renal circulation has been restored.[10]

CASE 3.—A 34 year old white woman was admitted to North Richland Hospital (medical service of Dr. J. O. Baugher), Feb. 3, 1949, complaining of nausea, vomiting, diarrhea, weakness and generalized aching pains of two days' duration.

Past History.—The patient had been a heavy user of alcoholic liquors for many years. She had undergone hysterectomy several years previously.

Present Illness.—For three weeks prior to admission she had been receiving treatment, including penicillin, for an infection of the upper respiratory tract. While intoxicated, she cleaned her trailer with carbon tetrachloride. Her complaints as already outlined followed shortly afterward and resulted in hospitalization two days later.

Physical Findings.—Notable findings were: blood pressure, 110 systolic and 50 diastolic; icterus of scleras, none; pharynx, injected; liver, palpable 1 to 2 fingerbreadths below the costal margin. There was some tenderness in the right upper quadrant of the abdomen.

Laboratory Findings.—The hemoglobin was 89 per cent of normal; the red blood cell count was 4,800,000; the white blood cell count, 20,100, with polymorphonuclear leukocytes 89 per cent, and lymphocytes, 11 per cent. No urine was obtained during the twelve hours of hospitalization prior to death.

Course.—The patient was given morphine and atropine on admission to control nausea and vomiting. Four hours later she received 2 grains (0.13 Gm.) of phenobarbital subcutaneously. Nausea and vomiting subsided, but the patient gradually became jaundiced, more drowsy and died in coma twelve hours after admission.

Autopsy.—Gross Observations: Skin, subcutaneous tissue, organs and body fluids were icteric. The lungs were congested. The liver weighed 1,890 Gm., and the cut surface was largely yellow, with dark punctated areas. The kidneys were pale. The right kidney weighed 192 Gm. and the left 240 Gm. There was mild old stenosis of the mitral valve.

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9. Peters, J. T.: Oliguria and Anuria Due to Increased Intrarenal Pressure, Ann. Int. Med. **23**:221 (Aug.) 1945. Reid, R.; Penfold, J. B., and Jones, R. N.: Anuria Treated by Renal Decapsulation and Peritoneal Dialysis, Lancet **2**:749 (Nov. 23) 1946. Abeshouse, B. S.: Renal Decapsulation: A Review of the Literature and a Report of Ten Cases, J. Urol. **53**:27 (Jan.) 1945.

10. Kolff, W. J.: The Artificial Kidney, J. Mt. Sinai Hosp. **14**:71 (July-Aug.) 1947. Murray, G.: Development of an Artificial Kidney: Experimental and Clinical Experiences, Arch. Surg. **55**:505 (Nov.) 1947. Frank, H. A.; Seligman, A. M., and Fine, J.: Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation, J. A. M. A. **130**:703 (March 16) 1946.

Microscopic Observations (Paul K. Lund, pathologist, Swedish Hospital, Seattle): The liver showed "extensive fatty degeneration as well as central necrosis. In many areas only a rim of normal liver tissue remained at the periphery of the lobule. The section of the kidneys showed cloudy swelling of both proximal and distal tubules, as well as some cellular necrosis. The epithelium of the descending tubules showed more advanced necrosis. There was some swelling of the endothelium of glomerular tufts, and hyaline casts were present in the descending tubules. The lungs showed marked passive congestion. The anatomic diagnosis was (1) acute yellow atrophy of the liver; (2) acute nephrosis; (3) passive congestion of the lungs; (4) old minimal mitral stenosis." Chemical studies of tissue from liver, spleen, heart and kidney were negative for the usually suspected heavy metals, alkaloids and carbon tetrachloride.

It was felt that carbon tetrachloride was the precipitating cause of death in this patient, in whom the liver was already in poor condition owing to acute and chronic alcoholism.

INDUSTRIAL CASES

The following brief reports of cases concern 4 employees of a subcontractor who were exposed to carbon tetrachloride fumes during a degreasing operation and whose complaints resulted in their being observed in Kadlec Hospital. Positive pressure air masks were supplied to operators where exposures might be excessive, and the mechanical setup was such that most of the work could be done with little exposure if care was used.

CASE 4.—*Present Illness.*—A 35 year old white man was admitted to Kadlec Hospital, Sept. 18, 1948, complaining of nausea and vomiting. He had worked with carbon tetrachloride in a degreasing operation for the past three months.

Past History.—This was not significant. A recent preplacement examination showed nothing remarkable.

Physical Findings.—The pupils were irregular, the left 1 mm. larger than right, and there was a suggestion of scleral jaundice. Icterus was questionable. The temperature was 100 F. There was an odor of carbon tetrachloride in the vomitus. The right upper quadrant of the abdomen was tender.

Laboratory Findings.—The urine contained albumin (1 plus) and was loaded with white blood cells; red blood cells ranged from 0 to 5 per high power field. The blood count was normal except for 12 per cent eosinophilic granulocytes. The icteric index was 28. Hanger's test for liver function (cephalin flocculation) showed a 2 plus reaction in forty-eight hours. On September 23 the urine was normal. The blood count showed 10 per cent eosinophilic granulocytes, and the icteric index was 4 units.

Course.—The patient was treated with penicillin, a high protein, high carbohydrate and low fat diet, liver extract, dextrose and a high vitamin intake. He improved and was discharged from the hospital on September 23.

Subsequent studies conducted by the outpatient department disclosed hypospadias, urethral stenosis and a small urinary bladder with thickened wall, all of which were obviously of long standing and contributed to the urinary findings and the elevation of temperature on admission.

CASE 5.—*Present Illness.*—A 38 year old white man reported for first aid, Sept. 22, 1948, complaining of nausea, nervousness and dyspnea. He had been

working on a carbon tetrachloride degreasing job for the past six weeks. He stated that one week previously a bucket of carbon tetrachloride was accidentally spilled on him. He was admitted to Kadlec Hospital on September 23, complaining of nausea, vomiting, headache, dizziness and abdominal pain.

Past History.—This was not significant. A preplacement examination, May 24, 1948, revealed nothing significant.

Physical Findings.—There was no evidence of icterus. Tenderness was present in the right upper quadrant of the abdomen.

Laboratory Findings.—The urine was alkaline, contained albumin (trace) and showed an occasional fine granular cast. The blood count was within normal limits. The icteric index was 3 units. Thymol turbidity was 12.5 units. The cephalin flocculation test was negative in forty-eight hours. The urine was normal on September 27.

Course.—The patient improved under the same treatment as was used in the cases already described and was discharged from the hospital on September 27. He continued to complain of gastrointestinal distress, anorexia, flatulence and nausea and subsequently gave a history suggestive of peptic ulcer and psychoneurosis of long standing. He had been rejected for military service because of a history of peptic ulcer.

CASE 6.—*Present Illness.*—A 39 year old white man reported for first aid, Sept. 18, 1948, complaining of nausea, vomiting, choking, anorexia, urinary frequency and dysuria. He was treated and permitted to go home. He returned on September 23 and was admitted to Kadlec Hospital. The patient felt that his complaints were due to carbon tetrachloride, although his exposure was known to have been of short duration. He was nervous, apprehensive and talkative—in fact, was quite fearful that he was going to die in first aid.

Past History.—This was not significant. A preplacement examination on Dec. 1, 1947 had shown nothing remarkable.

Physical Findings.—The abdomen was tender to palpation, with questionable enlargement of the liver, which was felt 1 fingerbreadth below the costal margin on deep inspiration. There was no scleral or dermal jaundice.

Laboratory Findings.—The urine was normal on September 23 and throughout the hospital stay. A complete blood count was within normal limits except for 7 per cent eosinophilic granulocytes. The eosinophilic granulocytes numbered 18 per cent on Dec. 1, 1947, 20 per cent on April 23, 1948 and 2 per cent on Sept. 28, 1948. A test for urinary urobilinogen was positive in 1:10 dilution; the icteric index was 9 units; thymol turbidity, 7.9 units; cephalin flocculation, 1 plus in forty-eight hours. Cloudy serum was noted. On Sept. 28, 1948 the total blood protein was 8.0 Gm. in 100 cc.; albumin, 4.7 Gm.; globulin, 3.2 Gm. and the albumin-globulin ratio was 1.4. The icteric index was 6 units. The cephalin flocculation test was negative in twenty-four and in forty-eight hours.

Course.—The patient improved under the same general treatment and was discharged from the hospital Sept. 28, 1948. He was quite apprehensive and nervous over his physical condition during and after his stay in the hospital.

CASE 7.—*Present Illness.*—A 58 year old white man reported for first aid, Sept. 20, 1948, complaining of nausea, vomiting, dizziness and a choking sensation which he attributed to carbon tetrachloride exposure of about two months' duration. His complaints continued, and he was admitted to Kadlec Hospital on September 28. The chief complaints on admission were polyuria, nocturia, irritation of the eyelids and anorexia.

Past History.—This was not significant. A preemployment examination, Nov. 12, 1947, revealed nothing remarkable.

Physical Findings.—There was bilateral conjunctival injection with questionable scleral jaundice. There were no other significant findings.

Laboratory Findings.—Urinalysis showed nothing of significance on September 20 and 28. A complete blood count revealed 14 per cent eosinophilic granulocytes; otherwise it was within normal limits. A test for urinary urobilinogen was negative in 1:20 dilution. Thymol turbidity was 7.5 units; the icteric index, 10 units; a sulfobromophthalein sodium test of liver function showed no abnormality; cephalin flocculation was 1 plus in 48 hours.

Course.—The patient improved under treatment and was discharged from the hospital on September 30. There were no other complaints relative to this illness.

During the degreasing operation, 51 employees reported for first aid with complaints which were probably caused by inhalation of fumes of carbon tetrachloride. The complaints in order of frequency were as follows: nausea 31, headache 22, vomiting 15, vertigo and dizziness 15, malaise 7, gastric upset 5, rawness of throat or of nasal passages 4, abdominal cramps 4, anorexia 3, nervousness 3, insomnia 2, nocturia 1, cough 1.

The urine specimens of the 51 affected persons were normal except for 1 that gave a 1 plus reaction for albumin, 2 with a few white cells and 1 with a few red cells. The blood counts were essentially normal with no abnormal red cell counts, three white cell counts over 12,000 and nine in which the eosinophilic granulocytes ranged from 4 to 9 per cent. Cephalin flocculation tests made with serum specimens from 31 men showed normal liver function except for one 1 plus, one 2 plus and one questionable flocculation. The icteric index was reported as follows: negative in 3 cases, doubtful in 1 and ranging from 4 to 10 units in 27.

The medical division advised management that this work should not be continued until working conditions were improved. Subsequent to this, trichloroethylene was substituted for carbon tetrachloride as a degreasing agent. The makeshift degreasing and ventilating equipment was replaced with a standard manufactured well ventilated degreasing tank especially designed for use with "tri chlor." The allowable air trichloroethylene concentration recommended is 200 parts per million parts of air, compared with 50 for carbon tetrachloride. Since this change was made, there is apparently almost no exposure, and we have had no complaints to date from any of the men working in this operation.

According to J. G. Townsend, Medical Director, Division of Industrial Hygiene, Federal Security Agency, Public Health Service,[11] an agreement drawn up in 1935 between the United States Public Health Service and manufacturers of carbon tetrachloride and/or similar

11. Townsend, J. G.: Personal communication to the authors, November 1948.

volatile chlorinated liquid hydrocarbons is the only attempt which has been made at a federal level to regulate the sale and distribution of carbon tetrachloride.[11] This agreement is quoted in full (italics ours):

We, the undersigned manufacturers of carbon tetrachloride and/or similar volatile chlorinated liquid hydrocarbons, hereby agree as follows:

1. That on all shipments of these materials from our plants *in excess of fifteen fluid ounces*, we will see that one of these warning labels is affixed to each individual container. *That the name of the particular material constituting the shipment will also appear in conspicuous letters either on a label*, affixed to each can, or stencilled on each drum or similar large-sized container.

2. That we will affix this warning label on all shipments in containers *in excess of fifteen fluid ounces of mixed solvents containing 24 per cent or over of any one of these chlorinated hydrocarbons* and that there will appear imprinted on the label or stencilled on the container, the words *"Contains more than 24 per cent by weight of Carbon Tetrachloride."* Or at the manufacturer's option, he may print the actual analysis of the fluid constituting the shipment.

3. That we will *notify all repackers and dealers* who purchase these chlorinated hydrocarbons from us, that "This product is sold under direct agreement with the United States Public Health Service, and *it is necessary to use the same labelling on all containers of a capacity in excess of fifteen fluid ounces* containing more than 24 per cent of carbon tetrachloride if repacked or reshipped." The above statement in quotations will be placed on all bills of sale.

4. We will use all proper means to bring about the universal use of this warning label and markings.

The recommended label is as follows:

WARNING! VOLATILE SOLVENT
VAPOR HARMFUL

Use with adequate ventilation.
Avoid prolonged or repeated breathing of vapor.
Avoid prolonged or repeated contact with skin.
Do not take internally.

Carbon tetrachloride is so poisonous that, according to Cairns,[12] 1 teaspoon (2 to 4 cc.) may constitute a fatal dose.

In case 2 cited in the foregoing report of cases, the vapor from one domestic type of fire extinguisher, one-half used, was almost lethal. United States Bureau of Mines Studies[5] indicated that under certain conditions the phosgene generated from 1 cup of carbon tetrachloride might be lethal.

Many persons have had personal experiences indicating that the fumes from a few ounces of cleaning fluid in a poorly ventilated place may prove very toxic. Then why is this poison referred to in such terms as "vapor harmful," "do not take internally," etc.? And why limit the warning labels to containers of 15 ounces (443 cc.) or more?

12. Cairns, F. J.: Carbon Tetrachloride Poisoning: A Fatal Case Following Accidental Ingestion of Carbon Tetrachloride, New Zealand M. J. 45:176 (June) 1946.

We feel that carbon tetrachloride sold in *any* quantity should be labeled and that the label should read

VOLATILE SOLVENT—POISONOUS (Usual skull and crossbones)
One teaspoonful taken by mouth may be fatal.
The fumes from one cupful breathed in a poorly ventilated place may cause death.
Use with adequate ventilation.
Avoid prolonged or repeated breathing of vapor.
Avoid prolonged or repeated contact with skin.
Do not take internally.

We believe that the present label gives the user a greater sense of security than is warranted and that many deaths occur from domestic use where no warning label is required.

SUMMARY AND CONCLUSIONS

Three cases of severe carbon tetrachloride poisoning are described. All were due to incidental single exposures not connected with an industrial operation. Two of the cases were fatal. Two were characterized by the lower nephron nephrosis syndrome. In treating patients for this condition, emphasis is placed on frequent chemical tests of the blood, with therapy aimed at combating acidosis, low calcium, low potassium and other developments as indicated, and limiting the fluid intake to equal the output, considering the decrease or the absence of output from the kidney for a limited period.

The 3 patients were heavy consumers of alcoholic beverages. Their histories add further to the almost overwhelming evidence of animal experiments and previous human cases that consumption of alcoholic liquor increases tremendously the risk of poisoning with carbon tetrachloride.

Four cases of mild industrial carbon tetrachloride poisoning and 51 cases of very mild exposure resulting from improper working conditions are discussed. The conditions were corrected by substituting trichloroethylene for carbon tetrachloride and using it in a properly designed custom-built degreasing unit.

A plea is made for national regulations requiring more stringent labeling of compounds containing carbon tetrachloride and that this be required on any volume, in contrast to the present regulations requiring labeling of quantities in excess of 15 fluidounces. Far less than this quantity inhaled or ingested will cause death.

Awareness on the part of physicians of the frequency of carbon tetrachloride poisoning together with reporting of all cases will be of value in indicating that the incidence of this condition is far greater than generally believed. Intensified efforts should be made to educate the public as to the dangers of the use of carbon tetrachloride.

THIRTY-FIVE CENTS PER COPY TWO SECTIONS WEDNESDAY, JUNE 29, 1988 OFFICE: 118 W. NINTH ST., AUBURN, IN

Bastian tragedy one of state's worst

By Star Staff

Tuesday's chemical accident at Bastian Plating Co. in Auburn is the worst Indiana factory mishap in recent memory.

Four men died when two chemicals mixed during a cleaning operation at the factory at 5 a.m. Tuesday.

A spokesman for the Indiana Occupational Safety and Health Administration said today that no one at the agency could recall a factory accident in Indiana causing as many as four fatalities.

Fred Ross said only construction accidents have caused a greater number of deaths at one time. The state's worst labor tragedy was a bridge collapse in Hammond that killed about a dozen people, he said.

Ross said IOSHA will take about two weeks to file its report on the Bastian Plating deaths. The agency sent a team of 4-5 experts to Auburn Tuesday. They will study the factory's safety procedures and toxic chemical practices.

DeKalb County Coroner Dr. William Hathaway, and Auburn Police Chief Buck Keesler, ordered the closing of the plant pending an investigation.

Kirk Carpenter, attorney for Bastian Plating, said the company spent Tuesday afternoon trying to cooperate with all the agencies investigating the tragedy — IOSHA, the State Fire Marshal, and the Indiana Department of Environmental Management.

"Local agencies have been so helpful," Carpenter said, praising the American Red Cross, Auburn Police, Auburn Fire Department and William Hathaway, M.D.

Carpenter said Bastian's owners are devastated by Tuesday's tragedy. "They just feel so bad for the families of these victims — all of these people," he said.

More than 50 persons work at Bastian, Carpenter said.

Tuesday's accident happened when the company was cleaning a tank to begin a change to safer chemicals, Carpenter said.

The company was trying to eliminate chemicals containing cyanide from its plant on West Fifteenth Street. The City of Auburn had complained about excessive amounts of cyanide and other chemicals in Bastian's sewage. A hearing on that issue has been postponed until July 15 at 10 a.m. in Auburn City Hall.

In trying to clean a zinc cyanide compound from a vat, employees improperly used muriatic acid, creating a deadly hydrogen cyanide gas, investigators said Tuesday.

One victim who survived the accident, Ron Alwood, was expected to be released today from Parkview Memorial Hospital in Fort Wayne. Patrick Cramer was to remain at Parkview for more testing.

Craig Fogle, the most seriously injured employee who survived the tragedy, remained in critical condition this morning at Parkview's intensive care unit.

Kim Miller, an Auburn Police officer who was hospitalized after entering Bastian Plating in a rescue effort Tuesday morning, is reported in stable and good condition at DeKalb Memorial Hospital.

Several other rescuers who were treated Tuesday after the tragedy have been released from DeKalb Memorial.

According to an Auburn physician, the Bastian workers who died in Tuesday morning's industrial accident succumbed to tissue asphyxiation.

"Although there is still some room for speculation as to whether the gas produced was cyanide, the effects are essentially the same," said the doctor, who asked that his name not be used.

"When the gas enters the body, it acts much like carbon monoxide, that is, it competes for oxygen," he said. "The gas creates a chemical block that prevents the red blood cells from releasing oxygen into the tissue. It binds the oxygen to the hemoglobin molecules, which results in tissue-asphyxiation."

The doctor added that depending on the dose, a person would be rendered unconscious within seconds and, unless immediate medical aid could be given, the person would die within three to five minutes. Tissue asphyxiation victims may appear to be breathing normally, but the air going into the lungs is of little help because the oxygen is not going where it's needed, he said.

The usual treatment for victims of cyanide gas or other toxic gases is to administer hyperbaric oxygen. Hyperbaric oxygen is pressurized in a tank and is forced into the victim's system to force blood through the chemical block. Hyperbaric chambers are often used to relieve discomfort experienced by deep sea divers or jet pilots who undergo severe atmospheric pressure changes.

The Auburn physician added that some other chemicals may be used in conjunction with the hyperbaric oxygen to dilate the blood vessels, allowing an easier flow of oxygen. Once the oxygen flow is returned, the body can begin flushing the chemical from the system.

He said that he wasn't sure if hyperbaric oxygen would be administered to Cramer and Alwood, two Bastian employees transferred to Parkview.

He added that since those two men didn't receive a large dose of the gas, chances were they would fully recover and there would be no long-term effects.

CHEMICAL CLEAN-UP — This Bastian Plating Co. employee was hosed down by Auburn firefighters Tuesday morning to remove hazardous chemicals, apparently a sludge of zi Four of his co-workers died from de the factory. (Star photo by Dave Kurt

Family won't forget victim of tragedy

By LEE SAUER

See page A10 for full obituary information on the accident victims.

Jeffery Link, a son who never forgot a special occasion and loved to work on cars, was one of four young men who died in Tuesday morning's chemical accident at Bastian Plating Co. in Auburn.

He was small-framed, blue-eyed, and 25 years old.

Jeff's mother, Linda Link, remembered her second of four sons as a person who liked to be alone and yet had lots of friends, as a quiet and thoughtful person.

"I have a pin that he bought me when he was 11 years old. It's not expensive, but its special to me," said his mother.

Jeff never forgot a birthday or an anniversary. He took his older brother's children out for morning donuts. He spent weekends with his youngest brother, 14-year-old Ben, and the two of them watched movies and played video games together.

"He was always going to take care of me and his dad," said Mrs. Link. She remembered the time when, right after the birth of her youngest son, some friends of the family offered to take the other boys with them on a nature trip. "He (Jeff) wasn't going to go mushroom hunting," she said. "He was going to take care of me and the baby."

Jeff loved spaghetti, or an Arby's Roast Beef washed down with a Jamocha shake.

He had several jobs before the past 3½ half years at Bastian.

When he was 13, he took a job with a bakery. "He was so

(Continued on page A10)

Training helped rescue handle chemical accide

By DAVE KNOPP

A sense of purpose and importance could not have been plainer at Tuesday's meeting of the DeKalb County Hazardous Materials Committee (HAZMAT).

Referring to Tuesday morning's four tragic deaths at Bastian Plating Co., DeKalb County Commissioner Bruce Gurtner said in the meeting's blessing, "I think the events of the day make it clear that the work of this committee is worthwhile."

Gurtner and other committee members asked Auburn Fire Chief Bill Walters numerous questions about how his department handled the poison gas incident which claimed the lives of four Bastian employees.

Walters was in charge of the rescue operation until he was required to be decontaminated. He said better identification of state and federal officials on the scene, including representatives from the Environmental Protection Agency, the Indiana Occupational Safety Hazard Association and the Indiana Department of Environmental Management, could have prevented some confusion.

"I didn't know one guy from the next," Walters said. "I don't know how you can make heads or their gear on, and went in pairs. Luckily, I had no injuries in my department."

About $8,000 worth of gear had to be disposed of due to contamination, Walters said. "I lost all my turnout gear, anything that had leather on it. They couldn't decontaminate it because the contaminant soaked right in."

Contamination al operation to be DeKalb County Em ical Service (EM Maier, EMS secreta lost quite a bit of equipment, includin We're taking inver find out just how

(Continued on

Law firm plans new downtown office building

By SUE MAWE

Plans for a new downtown office building and adjustments to the proposed new county welfare office were discussed at the Auburn Board of Zoning Appeals meeting Tuesday.

The law firm of Kruse, Kruse and Cherry is planning to construct a new office building in downtown Auburn to house the firm.

The proposed two-story build lot will be added behind the new structure.

Kruse appeared before the board to request a variance from present requirements on buildings in a community service district, specifically to waive a setback requirement of 67 feet from the edge of the property line along Cedar Steet. The board granted the request for a zero set back for the building and permission for

facted the Auburn Improvement Association to discuss how the new offices would change the downtown landscape, and he reported that they "are satisfied with what we're doing."

Mayor Burt Dickman said Kruse, Kruse and Cherry "should be commended for the fact that they went to the Auburn Improvement Association to ask their opinion. (The firm) has been very

Rescuers learnin to cope with stres

Emergency crews who worked on Tuesday's tragec tian Plating Co. will take part in a "stress debriefing" evening.

It is the third time since last fall that firefighters, medics and police have gathered to talk about ther after a tragic fatal accident.

"Basically, it's just a talk session," said Capt. Jeff the Auburn Fire Department. Stemen and Kay Stroc the DeKalb Emergency Medical Service, will lead cussion.

The stress is not new to emergency crews, but lear to cope with it is a new idea.

In the past, emergency crews had a macho, "it does me" attitude, Stemen said. But, he added, "maybe road it starts eating at them and they start taking it ou children."

He said rescuers often have a helpless feeling, "Y

Public Comments: **NAS Guidelines and Development of Additional Guidelines**

1. **Suggest development of "minimum" data set guidelines (by AEGL class)**

2. **Committee chose a less protective stance than recommended in NAS Guidelines**

    a. **Selection of LOAEL (vs. NOAEL) as basis for some AEGLs without use of additional safety factor, and with the use of inter- and intraspecies UF much lower than 10**

    b. **Departures from NAS guidelines - other standard guidelines are not sufficiently documented in the Technical Support Documents**

        (1) Particularly for data gaps in health effects of exposure to susceptible individuals (infants, children, elderly, chronically ill)

Public Comments: Definitions

1. **Define "notable discomfort" to better understand intent of AEGL-1**

2. **Shouldn't asthmatics be considered "hypersusceptible"**

3. **Definition of protected population unclear...**

    a. **protection of children and other susceptible or hypersusceptible populations is of great importance to the public and federal government**

    b. **not clear that AEGL process is being coordinated with other federal initiatives and state programs to insure that populations such as children are being adequately protected**

4. **Definition of susceptible individuals should not include human infants < 4 months of age (<0.4% of population)**

5. **Committee should develop definitions for susceptible and hypersusceptible individuals for a clear and consistent basis for such classifications (should be published for public comment)**

6. **Subcommittee was to be established to address sensitive and susceptible subgroups and present a preliminary report at the December, 1996 meeting. No mention of report in December 1996 "Draft Highlights"**

7. **AEGL definitions are obscure and do not reflect the customary definition of a health reference level (i.e. a level at which adverse health effects would <u>not</u> be expected to occur).**

8. **AEGL-1 should be protective of all potential adverse effects, including mild respiratory and other irritation effects**

Public Comments: **Reference Concentration Human Equivalent Concentration (RfC HEC) Methodology**

1. **RfC HEC methodology should be used for hydrazine**

    a. **No correction made with other chemicals when extrapolating from animals to man**

    b. **Compared to actual empirical data, the RfC HEC calculated LC50 values for fluorine in various species are significantly high**

    c. **Empirical LC50 values for hydrazine in various species should be compared to RfC HEC desired values to validate its use in hydrazine AEGL development**

Public Comment: Uncertainty Factors - (Inter and Intra species

1. Based on current and sound scientific principles (phosphine).

2. In Ethylene Oxide document - Use of UF of 3 for interspeciess extrapolation is inconsistent with a UF of 10 for some extrapolation during derivation of AEGL-2 - Does not follow NAS guidance: "An uncertainty factor of 10 is generally applied unless (1) dosimetric adjustments have been made (2) data are available to quantitate an animal to human extrapolation factor, (3) data on sensitive human subpopulations are available. None of these justifications were offered.

3. Has over-extrapolated down from animal data without recognizing and adjusting for sex-specific responses noted in all mammals.(Aniline)

4. Has over-extrapolated down from animal data by correcting for human infants < 4 months old (< 0.4% of population).

5. UFs of 3 have been applied for AEGLs for many chemicals with no scientific documentation for their justification.

    a. Scientific basis for using UF of 3 should be provided(for both inter and intra species)

    b. It is not clear how the larger relative exposure of children is being accounted for.

    c. Also unclear how sensitive individuals, such as asthmatics, who may differ in susceptibility, are being taken into account.

    d. Appears to be a fairly broad range of susceptibility among asthmatics. Horstman et al, found that there was a 7-fold difference in the range of concentrations of SO2 required to produce broncho construction.

Public Comments: Determination of NOAELs & LOAELs

1. **Believes they are based on current sound scientific principles (phosphine)**

2. **LOAELs rather than NOAELs used as the basis for AEGL derivation for many of the chemicals with Proposed AEGLs published in the FR Notice.**

    a. **NAS guidelines indicate that objective of the traditional toxicological risk assessment is to establish a threshold dose below which adverse health effects are not expected, or extremely unlikely to occur.**

    b. **NAS guidelines state that a step in the process is to determine the NOAEL and divide by the appropriate uncertainty factors.**

    c. **NAS guidelines state that an additional 10-fold uncertainty factor may be introduced when deriving AEGLs from appropriate LOELs or FELs.**

3. **AEGL-3 for fluorine was derived by dividing the LC 50 by 2. For dimethylhyrazine the LC 50 was divided by 3. No justification was given for the differences.**

Public Comments: Time Scaling

1. **Has not provided a Technical Support Document to prove that experimental scaling is a technically valid methodology and was used in a technically valid manner. EXAMPLE: "midpoint value of n=2 used ... because no exposure vs time data were available".**

2. **AEGL-l for hydrazine - time scaled from 24 hrs. to 4 & 8 hrs. and then flat lined to l hr. and l/2 hr. Should do one or the other, not both.**

3. **Dimethylhydrazine - the value of n is 0.84 and 0.80 in the rat and dog, respectively, yet Committee chose a value of n=1. Inconsistent with other chemicals where the actual value of n was used.**

4. **In scaling the exposure levels for the different time periods, the TSD has stated that "irritation is generally concentration dependent but not time dependent". Therefore, no scaling was done for nitric acid. However, in the case of fluorine and other chemicals where the AEGL-1 was based on irritation, the dose was scaled for each of the time periods. The reasons for these differences should be provided.**

Public Comments -- Phosphine

1. Agree here is inadequate data for AEGL-1

2. Agree with level, data and methods for AEGL-3

3. Disagree with level and methods for AEGL-2

   a. Calc. Based on 6 hr. exposure vs. 390 hrs. required for toxic endpoints observed.

   b. Recommend values based on 1/2 (i.e., 195 hrs.) Of rat's exposure time.

4. For AEGL-2 and AEGL-3 an UF of 3 was used for interspecies extrapolation since "the rat was the most sensitive species". However, as indicated by NAS "in the absence of the most relevant species, data from the most sensitive species should be used."

   --- This should be considered a rule for proper scientific evaluation and data selection, not a justification for an UF.

Public Comments --- 1,2-Dichloroethene

1. In deriving AEGL-1 it is not clear that a UF of 3 can account for the range in susceptibility for narcosis based on a single human subject.

   a. TSD should indicate the number of subjects and justify how a small sample is expected to represent a population of responses with a UF of only 3.

2. AEGL-2 level based on slight dizziness in human study (1936) requires further explanation of the justification ("the mode of action and similarity of response to this chemical") in terms of the

narrow range of this response inferred from the UF of 3.

3. No discussion or justification for using anUF of 3 (vs. The standard factor of 10) for intraspecies variability in deriving AEGL-3. Especially unclear since it appears cause of death may be direct cardiac failure rather than neurological effects cited for AEGL-1 and 2.

Public Comments --- Methylhydrazine

1. Believes an UF of 10 should be used for AEGL-2 and 3 rather than a UF of 3 for intraspecies variability

    a. UF of 3 for intraspecies variability should provide the scientific basis for the justification of an UF of 3 in the case of a steep dose-response curve.

2. TSD refers to calculation of carcinogenic risk of 1 in 10, 000

    a. Bases for establishing this risk and the concentration producing this risk should be provided.

    b. It is not clear why this level of risk is considered acceptable for the general public.

Public Comments --- Dimethyl hydrazine

1. n values derived for dimethyl hydrazine are 0.84 and 0.80 in the rat and dog, respectively, yet a value of n = 1 was used for toxic scaling . For all other chemicals, the actual calculated value of n was used.

2. AEGL-2 based on LOAEL not adjusted to NOAEL

    a. NAS guidelines indicate the traditional toxicological risk assessment objective is to establish a threshold below which no adverse health effects are expected to occur.

b. NAS guidelines state that the NOAEL is to be determined

c. NAS guidelines state that an additional 10-fold UF may be introduced when deriving an AEGL-2 or AEGL-3 from appropriate LOAEL or FELs. No discussion/justification is provided for not applying an additional UF. How can the Committee be sure that the concentration in the dog study represents a threshold for the effects in that species?

3. An UF of 3 was used for interspecies extrapolation to derive AEGL-2, yet no explanation was presented to indicate how the species tested represent likely human responses.

4. No scientific justification provided for the adjustment of an LC_{50} to a non-lethal level.

5. No scientific justification given to indicate how the species tested represent likely human responses to lethal effects and thereby justifies a UF of 3 for interspecies extrapolation for deriving AEGL-3.

Public Comments --- Fluorine

1. UF of 3 used in AEGL-1 for intraspecies variability with no scientific basis for the conclusion (fluorine acts corrosively with tissues of respiratory tract and is not likely to differ among individuals, including sensitive individuals) provided.

2. In scaling the values of AEGL-1 for different exposure time periods there was a rounding of values (at mildly irritating concentrations there is a tolerance to irritating gases.)

3. Not clear if AEGL-2 is based on an NOAEL or LOAEL production of mild lung congestion in mice). Needs clarification.

4. No UF applied for interspecies differences for AEGL-2 and AEGL-3. Justification given does not seem sufficient (not clear how potential diference in human susceptibility has been accounted for).

5. UF of 3 applied for intraspecies differences for AEGL-2

   a. Unclear how asthmatics are being taken into account

   b. Unclear how the larger relative exposure of children is being taken into account.

6. The addition of a modifying factor of 2 appears contradictory (applied for limited database but not variability for species diferences or variability in human response).

7. AEGL-3 based on dividing LC_{50} by 2, while the procedure for dimethyl hydrazine involved dividing the LC_{50} by 3. No justifiction was given for the difference.

Public Comments --- Aniline

1. Committee has over-extrapolated down from animals to humans

   a. Failed to recognize and adjust for sex-specific resonse noted in all mammals.

   b. Failure to correct for human infants < 4 months of age as "hyper susceptible" individuals

   c. Failureto make adequate allowance for a "floor" for exposure related cause and efect (i.e., < 15% MetHb asymptomatic).

   d. Failure to account for very short half-life of MetHb andcalculate the concentration level(s) sufficient to maintain a stable level of MetHb elevation against which there is a need to protect.

2. Committee placed excessive reliance on selected experimental (single male rat study) test results without:

   a. Involving producers re: Available data base

b. Trying to correlate the animal and human data (rather than dismissing the human data as unreliable)

c. More thorough effort to obtain additional human data (some of which is in EPA files).

3. AEGL-1 level based on LOAEL (elevation of MetHb from 1.1% to 22% causing cyanosis)

   a. NAS guidance states an additional 10-fold UF may be used when deriving an AEGL-1 from a LOAEL.

4. AEGL-2 and AEGL-3 derived using a 3-fold intraspecies UF to protect against hemolysis and lethality, respectively

   a. Should be more scientific justification for UF of 3 (e.g., are borderline anemics protected?)

   b. Document states human data is limited but is not clear on why it is limited.

5. Time scaling factor of 2 used for AEGL-2 and AEGL-3

   a. In spite of noted extreme steepness of dose-response curve

   b. No scientific extrapolation for the selection of n = 2.

Public Comments --- Chlorine

1. Disagree with 1 hr. AEGL-2 of 2.0 ppm,

   a. ERPG-2 is 3.0 ppm and has become an industry established and standard

   b. Both ERPG-2 and AEGL-2 based on some study (Rotmanietal)

c. AEGL committee makes no effort to explain why their value differs

d. AEGL-1 and 3 correspond exactly to ERPG-1 and 3

2. Disagree re the proposed AEGL-2 -- 1 hr. of 2.0 ppm

   a. ERPG-2 established on same basis and is 3.0 ppm

   b. EPPG-2 is the established and recognized standard in industry and government

   c. Likely that AEGL-2 and ERPG-2 based on same tox data (Rotman et al). "If based on the same data, we see no justification to reduce the level."

3. Deep concern for the basis of developing AEGL-2 for Chlorine.

   a. Committee making decision re astmatic in rotman et all paper that is counter to the findings of the authors.

   b. Asthmatic responses did not affect proposed AEGL-1 and AEGL-3 values

   c. Committee should develop definition for susceptibile and hyper susceptibility individuals for a clear and consistent basis for such classifications

   d. Proposed AEGL-2 value should be withdrawn until formal criteria are esablished by the Committee

4. AEGL-1 and AEGL-2 based on one sensitive asthmatic individual in a study.

   a. How does this basis justify the absence of a UF to protect a wide range of sensitive individuals in the population?

(1) Asthmatic may differ in susceptibility
(2) children breath in a greater proportion than adults

5. FR notice indicates asthmatics in study had measurable pulmonary functions parameter changes. Why is this effect not considered adverse in established AEGL-1.

6. Not clear why an asthma attack, which readily may be a life threatening condition, is used as the basis for AEGL-2. Also, why is no margin of safety included? E.g., AEGL-2 should be 0.5 ppm (level that did not produce an asthma attack) rather than 1.0 ppm.

7. FT notice indicates mouse is most sensitive mamal, yet humans respond to 0.5 to 1.0 ppm range vs. Effects in mice at 150 ppm. It is inclear how the conclusion that the mouse is most sensitive was reached.

8. AEGL-3 was derived using Ufs of 3 for inter- and intra- species differences

   a. Unclear how reported small difference between mouse/rat equates to rat/human

   b. UF of 3 for intra-species justified by similarity of chemical reaction with tissues. Unclear how variations in asthmatics and larger relative exposure of children are being taken into account.

Public Comments --- Nitric Acid

1. Ufs of 3 applied for intraspecies variation in AEGL-1 and AEGL-2

   a. No scientific basis provides for conclusion in case of AEGL-1

   b. No justification for AEGL-2

   c. Not clear how the larger relative exposure of children is being accounted for

   d. Unclear how sensitive individuals such as asthmatics who may

differ in susceptibility are being taken into account.

2. AEGL-2 is based on a LOAEL for human effects

   a. Objective of traditional toxicological risk assessment is to establish a threshold dose below which adverse health effects are not expected, or are extremely unlikely, to occur.

   b. NAS states that NOAEL should be determined

   C. NAS states that an additional 10-fold UF may be introduced when deriving an AEGL from a LOAEL.

3. No time scaling done since "irritation is generally concentration dependent but not time dependent." However, for chemicals where AEGL-1 is based on irritation, such as fluorine, the dose was scaled for each of the time periods. The difference in the two approaches should be explained and justified.

4. Not clear how the AEGL-3, which is based on a diferent chemical, nitrogen dioxide, can be derived using a UF of 3 for intraspecies variability. Further, since the incorrect UF value seems to have been used for AEGL-2, lower AEGL-2 values would have eliminated the excuse not to use UFs with AEGL-3 since the AEGL-3 values would be below the values derived for AEGL-2.

Public Comments --- Hydrazine

1. All AEGLs endorsed

   a. AEGLs appropriate -- CMA

   b. Agree with key study -- CMA

   c. Suggest TSD include description of chamber atmosphere analysis

2. AEGL values for hydrazine flawed

a. AEGL-1 time scaled to 4 and 8 hrs, flat lined ½ and 1 hr

b. RfC HEC should not be used with hydrazine

3. LOAEL was used as the basis for AEGL-1 and AEGL-2

   a. Does not follow objectives of traditional toxicological risk assessment to establish threshold below adverse effects not expected, or extremely unlikely to occur

   b. NAS guidelines state that NOAEL should be determined

   c. NAS guidelines state that an additional 10-fold UF may be introduced when deriving AEGLs from a LOAEL rather than a NOAEL

4. UF values of 3 were used for both inter- and intraspecies extrapolation inthe derivation of AEGL-1, but no scientific documentation is provided for their justification.

5. An intraspecies UF of 3 was used in the derivation of AEGL-2 and AEGL-3 with no chemical specific scientific justification.

6. The lethal level for AEGL-3 is based on an LC 01 rather than a benchmark calculation. A new procedure, not described elsewhere, apears to be introduced without scientific verification.

7. The document referes to the calculation of carcinogenic risk. The risk level and the basis should be provided.

Public Comments: Ethylene oxide

1. Recommends use of mathematical dose-response models rather than RfD-RfC approach

    a. Adequate (large) amount of data available

    b. Benchmark concentration modeling has advantages over RfD-RfC

        (1) Uses entire dose-response curve

        (2) Sensitive to the number of animals in the study

        (3) Could be used for those exposure periods where adequate studies are available

        (4) Can be used for both lethan and non-lethal data

    c. Categorical regression models could be used

        (1) Combines data from several studies

        (2) Can use several types of data (dichotomous, continuous, descriptive)

        (3) No duration extrapolations are necessary (model develops relationship between response severity, concentration, and duration of exposure)

        (4) Can be used for both lethal and non-lethal data

    d. 1993 NAS guidance indicates that benchmark concentration method would be developed to compare to the NOAEL

    e. Presents a table comparing categorical regression analysis to Proposed AEGLs. (Exposure concentrations converted to HEC). Relates to a concentration at which there is a 10% chance of having the effect.

f. Editorial errors in the TSD

g. The effects and supporting data used to derive AEGL-2 and AEGL-3 are unclear

h. Should use the better study (Sega, 1988, 1991) for genetic toxicology if this serves as the basis for AEGL-2

i. Should consider the better study (Embree et al, 1977) for reproductive effects if this serves as the basis for AEGL-3

j. Questions on rationale (P. 64) of dog vs. rat data

k. Use of UF of 3 for interspecies extrapolation is inconsistent with a UF of 10 for same extrapolation during derivation of AEGL-2. (See Generic UF Factors). Does not follow NAS guidelines

2. The AEGL-2 was derived based on the LOAEL (ens depression, diarrhea, and eye and respiratory tract irritation in rats @ 1000 ppm for 4 hrs.)

   a. No explanation for not applying the additional safety factor

   b. Not clear how the Committee can be sure that the concentration in the rat study represents a theshold for the effects in that species

   c. The LOAEL of 1000 ppm is above reported lethal levels cited in FR

3. AEGL-2 levels of 19 ppm (8 hrs) and 33 ppm (4 hrs) are close to reported level (50 ppm, 6 hrs) that reportedly produced reproductive and developmental toxicity.

   a. Exclusion of data not discussed in FR notice

4. An UF of 3 was applied for interspecies sensitivity because modes of action are likely to be similar across species, but no documentation or

citation is provided

5. Calculation of carcinogenic risk was made for 1 in 10,000

   a. Why is this risk acceptable for the general population?

   b. A risk of 1 in 100,000 is related to approximately 35 ppm for 4 hrs, essentially identical to AEGL-2

6. The AEGL-3 is based on an LC_0. It is not clear why a benchmark dose calculation was not used instead of a new procedure, not described elsewhere, and has been introduced without scientific verification.

PROPOSED BROMINE AEGLs

March 10, 1998

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Zarena Post

Chemical Reviewers:
Larry Gephart
Doan Hansen

Attachment 6

BROMINE

- PROPERTIES: Liquid, readily vaporizes at room temperature
  highly reactive dark reddish-brown gas
  moderate water solubility

- PRODUCTION CAPACITY: 243,000 metric tons (1993)

- USES: Bromine-containing agricultural chemicals, water disinfection, bleaching of fibers, medicinal bromine compounds, dyestuffs, flame retardants, drilling fluids, gasoline additive

- TOXICITY CONCERNS:
  Skin, eye, respiratory tract irritant
  lower concentrations scrubbed in nasal passages, upper respiratory tract
  higher concentrations reach lungs producing pulmonary edema, necrosis

BROMINE

- AVAILABLE DATA

Human data

deaths have occurred from accidental exposures

irritant effects - much information is anecdotal

accident in Geneva, Switzerland (Morabia et al., 1988)
irritant effects
concentrations of 0.2-0.5 ppm measured at an undefined time

exposure of volunteers to bromine and chlorine (Rupp and Henschler, 1967)
bromine more irritating than chlorine
values for chlorine too low compared with later, well-conducted studies

BROMINE

Animal studies

Two lethality studies, one species (mouse)

Schlagbauer and Henschler (1967):
- chlorine LC_{50} values not in line with other studies
- bromine values appear correspondingly low
- based on 30-min LC_{50}, chlorine was 1.4 times more toxic than bromine

Bitron and Aharonson (1978):
- "delayed deaths"
- animals were restrained
- based on 30-min LC_{50}, chlorine was twice as toxic as bromine

BROMINE

Irritant effects of halogens based on water solubility?

Fluorine: reacts with water

Chlorine: 6-10 g/L

Bromine: 35 g/L

BROMINE

Subjective responses to chlorine and bromine (Rupp and Henschler, 1967)
healthy students (20)
half-hour exposures

	Chlorine (ppm)	Bromine (ppm)
Odor threshold	0.02-0.05	>0.01
Identification	0.1	>1

MOUSE LETHALITY DATA FOR CHLORINE AND BROMINE		
Chemical	30-Minute LC_{50}	Reference
Chlorine	203 127	Bitron and Aharonson, 1978 Schlagbauer and Henschler, 1967
Bromine	424 174	Bitron and Aharonson, 1978 Schlagbauer and Henschler, 1967

Bitron and Aharonson used two time periods from which an n value of 2.2 was derived. ($C^{2.2} \times t = k$)

The n value for chlorine is 2.

BROMINE AEGLs

Two Options

1. Do not derive AEGL-1 and AEGL-2 values until more data are available
   Suggest mouse RD_{50} (can compare with chlorine RD_{50})

   Use the more realistic lethality study (Bitron and Aharonson, 1978) to set the bromine AEGL-3

2. Use the comprehensive data base of chlorine studies to set bromine levels
   Divide chlorine levels by ~ 2 to account for greater irritancy of bromine

   Use the more realistic lethality study (Bitron and Aharonson, 1978) to set the bromine AEGL-3

BROMINE

Chlorine study with human volunteers - Rotman et al. 1983

Subjects:
- eight healthy male subjects
- one subject with "allergic rhinitis"

Effects:

0.5 ppm for 4 hours:	no/slight effects in 8/9 subjects transient changes in pulmonary functions in 1/9 subjects
1.0 ppm for 4 hours:	transient changes in pulmonary functions in 8/9 subjects asthmatic-like response in 1/9 subjects

Chlorine study with human volunteers - Rupp and Henschler 1967

Subjects:
- healthy students

Effects:

0.05 ppm for 30 minutes?	irritation
0.5 ppm for 15 minutes?	pain

PROPOSED CHLORINE AEGLs

Classification	Exposure Duration			
	30-Minute	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	1.4 ppm (4.1 mg/m^3)	1.0 ppm (2.9 mg/m^3)	0.5 ppm (1.5 mg/m^3)	0.5 ppm (1.5 mg/m^3)
AEGL-2 (Disabling)	2.8 ppm (8.1 mg/m^3)	2.0 ppm (5.8 mg/m^3)	1.0 ppm (2.9 mg/m^3)	0.7 ppm (2.0 mg/m^3)
AEGL-3 (Lethal)	28 ppm (81 mg/m^3)	20 ppm (58 mg/m^3)	10 ppm (29 mg/m^3)	7.1 ppm (21 mg/m^3)

PROPOSED BROMINE AEGLs

Classification	Exposure Duration			
	30-Minute	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	0.5 ppm (3.3 mg/m^3)	0.5 ppm (3.3 mg/m^3)	0.25 ppm (1.6 mg/m^3)	0.25 ppm (1.6 mg/m^3)
AEGL-2 (Disabling)	1.5 ppm (9.8 mg/m^3)	1.0 ppm (6.5 mg/m^3)	0.5 ppm (3.3 mg/m^3)	0.5 ppm (3.3 mg/m^3)
AEGL-3 (Lethal)	17 ppm (111 mg/m^3)	12 ppm (78 mg/m^3)	6.5 ppm (42 mg/m^3)	4.8 ppm (31 mg/m^3)

EXOGENOUS SOURCES

Auto exhaust

Electric utilities

Industrial boilers

Gas stoves

Unvented space heaters

Kerosene heaters

Wood stoves

Tobacco products (400-1000 ppm)

INDUSTRIAL USES OF NO

Intermediate in production of nitric acid from ammonia

Bleaching of rayon

Stabilizer for propylene and methyl ether

Formation of nitrosyl carbonyls

ENDOGENOUS ACTIONS OF NO

Regulator of functions of cardiovascular, immune, and nervous systems

Relaxation of vascular smooth muscle

THERAPEUTIC USES

ARDS

Persistent pulmonary hypertension of the newborn

Pulmonary hypertension
- congenital heart disease
- diaphragmatic hernia
- thoracic organ transplantation
- idiopathic
- COPD

TOXICITY

Methemoglobin formation

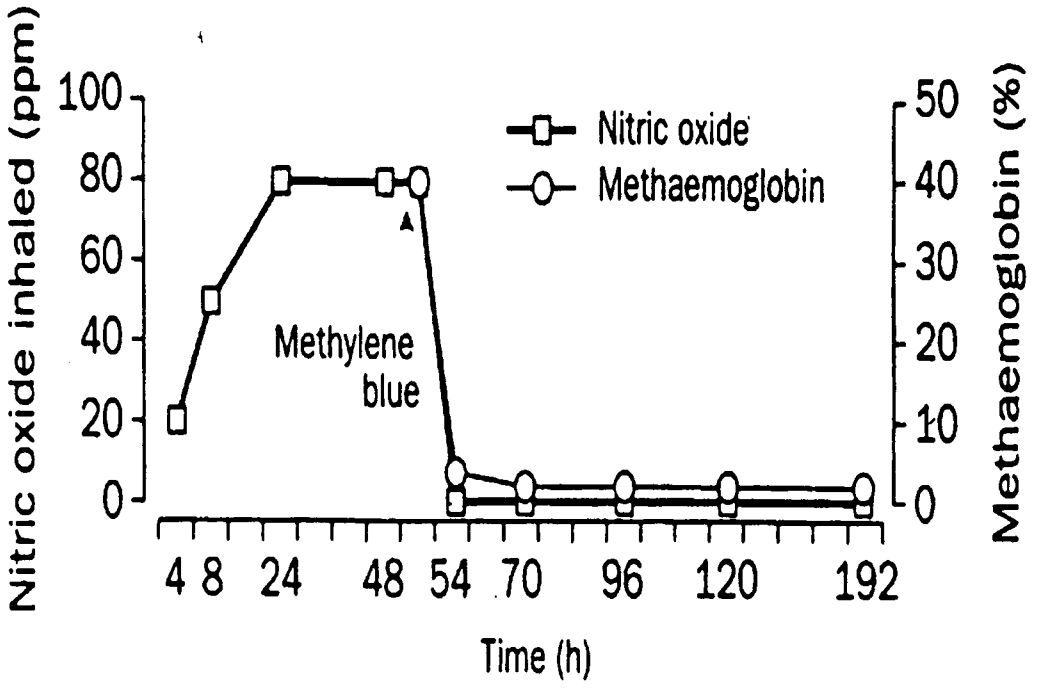
Conversion to NO_2

SIGNS AND SYMPTOMS IN HUMANS ASSOCIATED WITH METHEMOGLOBIN CONCENTRATIONS	
Methemoglobin Concentration (%)	**Signs and Symptoms**
1.1	Normal level
1-15	None
15-20	Clinical cyanosis (chocolate brown blood); no hypoxic symptoms
30	Fatigue; recovery without treatment
20-45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45-55	Decreased level of consciousness
55-70, ~60	Hypoxic symptoms: semistupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia; high incidence of mortality
>85	Lethal

Sources: Kiese, 1974; Seger, 1992

SUMMARY OF HUMAN DATA FOR NO EXPOSURE

Concentration	Duration	Effects	Ref.
??	2 min	cyanosis; delayed pulmonary edema; death	Clutton-Brock, 1967
80 ppm	26 hr	40% metHb; human infant	Nakajima et al., 1997
10-80 ppm	10 min - 24 hr	decreased PAP in infants and children	(several)
80 ppm	6-108 hr	<10% metHb; organ transplantation and pulmonary hypertension	Adatia et al., 1994; Wessel et al., 1994
80 ppm	10 min	modulation of methacholine-induced bronchoconstriction; increased airway conductance in asthmatics	Högman et al., 1993a
0.5-40 ppm	20 min-48 hr	therapeutic reduction of pulmonary artery pressure in ARDS patients	Manktelow et al., 1997; Troncy et al., 1997b


Nitric oxide inhaled (ppm)
100
80
60
40
20
0
Nitric oxide
Methaemoglobin
Methylene blue
50
40
30
20
10
0
Methaemoglobin (%)
4 8 24 48 54 70 96 120 192
Time (h)

SUMMARY OF ANIMAL DATA FOR NO EXPOSURE

Concentration	Duration	Species - Effects	Ref.
5000 ppm 20,000 ppm	25 min 7-50 min	dogs - death; metHb; pulmonary edema due to NO_2	Greenbaum et al., 1967
40-80 ppm	≤ 40 min	dogs - decreased PAP in canine model of lung injury	Channick et al., Romand et al., Putensen et al., 1994; Zwissler et al., 1995; Chen et al., Hopkins et al., 1997
1000 ppm	30 min	rats - 11/20 died; cyanosis	Stavert and Lehnert, 1990
500-1500 ppm	5-30 min	rats - no evidence of lung injury	Stavert and Lehnert, 1990
20 ppm	6 hr	rabbit - decreased PAP in model of lung injury	Nishina et al., 1997
10-80 ppm	≤ 30 min	pigs - decreased PAP in model of lung injury	Goldstein et al., Hillman et al., 1997; Shah et al., Nelin et al., 1994
1000 ppm	15 min	pig - 20% metHb	Nelin et al., 1994
5-80 ppm	≤ 3 hr	sheep - decreased PAP in model of lung injury	Frostell et al., 1991; DeMarco et al., 1996
512 ppm	20 min	sheep - 11% metHb	Dyar et al., 1993
100 ppm	40 hr	rats - no evidence of lung injury	Garat et al., 1997

Proposed AEGL-1 for Nitric Oxide

Key studies: Adatia et al., 1994; Wessel et al., 1994

Toxicity endpoint: ~10% metHb after therapeutic use of 80 ppm for 6-108 hrs

Scaling: none

Uncertainty factors: none

Proposed AEGL-1 Values for Nitric Oxide (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	80 [100]	80 [100]	80 [100]	80 [100]

Proposed AEGL-2

No relavent human data.

No relavent animal data.

Possible AEGL-3 Derivation

Key study: Stavert and Lehnert, 1990

Toxicity endpoint: 11/20 rats died after exposure to 1000 ppm for 30 min; approximate LC_0 is 333 ppm

Scaling: $c^n \times t = k$, $n = 2$

Uncertainty factors: none

AEGL-3 Values:

30 min	1 hr	4 hr	8 hr
333 ppm	235 ppm	118 ppm	83 ppm

Problems:

no uncertainty factors applied

4- and 8-hr approach therapeutic concentration

concentration-respose data not available

saturation kinetics of rhodanese unknown

species variability unknown

Possible AEGL-3 Derivation

Key study: Nakajima et al., 1997

Toxicity endpoint: 40% metHb after 26 hours of 80 ppm

Scaling: $c^n \times t = k$, $n = 2$

Uncertainty factors: none

AEGL-3 Values:

30 min	1 hr	4 hr	8 hr
577 ppm	408 ppm	204 ppm	144 ppm

Problems:

extrapolation from long time period to relatively short time period

not supported by animal data

30 min and 1-hr too high as compared to estimated rat LC_0 of 333 ppm

11% metHb in sheep after exposure to 512 ppm, 20 min

20% metHb in pigs after exposure to 1000 ppm, 15 min

not supported by human data

~10% metHb after therapeutic use of 80 ppm for 6-108 hrs

concentration-response data not available

saturation kinetics of rhodanese unknown

Possible AEGL-3 Values for Nitric Oxide (ppm [mg/m^3])				
30-min	1-hr	4-hr	8-hr	Endpoint (Ref.)
577 [721]	408 [510]	204 [255]	144 [180]	40% metHb after 80 ppm for 26 hr (Nakajima et al., 1997)
333 [416]	235 [294]	118 [148]	83 [104]	estimated LC_0 (Stavert and Lehnert, 1990)

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CHLOROMETHYL METHYL ETHER, TECHNICAL GRADE

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DERIVATION OF CONCENTRATION-RESPONSE RELATIONSHIP ($c^n t = k$) FOR CHLOROMETHYL METHYL ETHER

Key Study: Hake and Rowe, 1963 (unpublished data from The Dow Chemical Company). Exposing rats to 2000 ppm CMME (purity not reported) for 30 minutes or 100 ppm for 4 hours was "dangerous to life." Exposures were 100, 200, 500, 1000, 2000, 5000, or 10,000 ppm.

Calculation of n: $c^n t = k$

$$n = \frac{\log (time_2/time_1)}{\log (conc_1/conc_2)} = \frac{\log (240/30)}{\log (2000/100)} = 0.694$$

On further consideration, with input from the chemical manager and reviewers, this data was deemed **NOT SUFFICIENTLY RELIABLE TO BE USED AS THE BASIS FOR DETERMINING N**. *In the absence of chemical-specific data*, the default value **n = 2** was used for the concentration-time relationship (ten Berge et al., 1986). Therefore, will use: **$c^2 \times t = k$**

ADDITIONAL SUPPORT FOR n = 2:

LC_{50} for 2 hr **CMME** exposure of mice = 313 ppm (Toxic Parameters., 1982)
LC_{50} for 6 hr **BCME** exposure of mice = 5.3 ppm (Leong et al., 1971); **if neglect contribution of CMME to toxicity, and BCME is extrapolated to 100% CMME, then**

~1% BCME in CMME yields n = -2.09
~3% BCME in CMME yields n = 2.07
~5% BCME in CMME yields n = 1.01
~10% BCME in CMME yields n = 0.62

AEGL-1 VALUES FOR TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (107-30-2)			
30 minutes	1 hour	4 hours	8 hours
(No studies available within scope of AEGL-1 definition)			
AEGL-1 values were not derived because there were no studies of appropriate exposure duration or that had endpoints consistent with the definition of AEGL-1. [Additionally, it was not appropriate to calculate AEGL-1 values because the derived AEGL-2 (and possibly AEGL-3) values were probably below the level of sensory detection in humans.]			

AEGL-2 VALUES FOR TECHNICAL GRADE CMME (Drew, et al., 1975)				
Scaling	30 minutes	1 hour	4 hours	8 hours
n = 2	0.12 ppm	0.082 ppm	0.041 ppm	0.029 ppm

Scenario: Rats (25) given 30 six-hour exposures to 1 ppm **tech-CMME** and held for life had regenerative hyperplasia (2/13) or tracheobronchial squamous metaplasia (2/13); cause of two deaths (exposure days 16, 22) was unknown; AEGL-2 was based on one 6-hour exposure.

Total uncertainty factor: 10
Interspecies: 3 -(rats to humans)- Key study was multiple exposure; CMME is believed to be a proximal toxin and metabolism is unlikely to be significantly involved in its efficacy.
Intraspecies: 3 -(sensitive humans)- CMME metabolism is unlikely a factor.

Modifying Factor: 3 - Variability in the BCME content of technical grade CMME

Note: Although this study has the drawback that it involves multiple exposures, it has the benefit of lifetime observation of the animals, which is pertinent for a suspected cancer-causing agent.

Compare to TSD:

n = 1; UF= 30	0.40 ppm	0.20 ppm	0.050 ppm	0.025 ppm

Alternate calculation based on 6-month **BCME** NOEL study (Leong et al., 1981)

n = 2; UF= 10	0.061 ppm	0.043 ppm	0.022 ppm	0.015 ppm

AEGL-2 VALUES FOR TECHNICAL GRADE CMME

*Study **supporting** assertion that one 6-hour exposure to 1 ppm technical grade CMME **will not cause mortality** in rats (Laskin et al. 1975)*

- Lifetime inhalation of 1 ppm technical grade CMME (6 hrs/day, 5 days/wk; by 74 male rats and 90 hamsters.
- No effect on mortality or body weight gain in either species.
- **Rat** respiratory mucosa showed a marked increase in the incidence of tracheal squamous metaplasia and bronchial hyperplasia compared to control (74 sham exposed) rats, as well as one lung squamous cell carcinoma and one nasal esthesioneuroepithelioma (0 in controls).
- **Hamsters** had few mucosal differences from the 80 sham exposed controls, although they had more peripheral bronchoalveolar changes including metaplasia and alveolar cell atypia (with nuclear abnormality). One exposed hamster had a lung adenocarcinoma and one had a tracheal squamous papilloma (0 in controls).

POTENTIAL ALTERNATE AEGL-2 VALUES FOR TECHNICAL GRADE CMME BASED ON BCME EXPOSURE

Key study: Leong et al. (1975, 1981) rat and mouse **6-months** exposure (**6 hr/day**, 5 days/week) to 1 or 10 ppb BCME vapor; no tumorigenic effects or early mortality were seen (but exposure to the next higher concentration, 100 ppb, caused both). **BCME ÷ 0.08 ⇒ CMME; used 12 hrs. as exposure time; 10 ppb as exposure concentration**

Scaling: $C^2 \times t = k$ (ten Berge et al., 1986)

Uncertainty factors: 10: 3 for intraspecies (among humans) variability
3 for interspecies (rat to human) variability

AEGL-2 VALUES FOR TECHNICAL GRADE CMME (ppm) BASED ON BCME EXPOSURE IN RATS					
Scaling	UF	30 minutes	1 hour	4 hours	8 hours
n = 2	10	0.061	0.043	0.022	0.015

AEGL-3 VALUES FOR TECHNICAL GRADE CMME (Drew, et al., 1975)					
Scaling	UF	30 minutes	1 hour	4 hours	8 hours
n = 2	30	1.8 ppm	1.3 ppm	0.65 ppm	0.46 ppm

Scenario: Rat 7-hr exposure LC_{50} study (>10 males/conc.: 12.5, 26, 42, 54, 70, 141, or 225 ppm t-CMME); observed 14 days. Rats that died, and to a lesser degree, rats surviving to 14 days, had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis. LC_{01} (14.8 ppm) obtained by probit analysis was used to derive AEGL-3 values.

Total uncertainty factor: 10

Interspecies: 3 -(rats to humans)- Rat and hamster had similar 7-hour LC_{50} values for technical grade CMME, which is believed to be a proximal toxin and metabolism is unlikely to be significantly involved in its efficacy.

Intraspecies: 3 -(sensitive humans)- CMME metabolism is unlikely a factor.

Modifying Factor: 3 - Variability in the BCME content of technical grade CMME

Note: TSD calculation had an additional modifying factor of 3 to account for potential carcinogenicity of t-CMME.

n = 1	UF=100	2.1 ppm	1.0 ppm	0.26 ppm	0.13 ppm

SUMMARY OF AEGL VALUES FOR TECHNICAL GRADE CMME UF = 30 n = 2 [values in **ppm**]					
Classif.	**30 min.**	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
AEGL-1	(No studies available consistent with AEGL-1 definition)				
AEGL-2	0.12	0.082	0.041	0.029	30 six-hr exp. to 1 ppm tech-CMME; tracheal or bronchial squamous metaplasia; hyperplasia (Drew et al.,1975)
AEGL-3	1.8	1.3	0.65	0.046	7-hour LC_{01} (14.8 ppm) in rats (Drew et al., 1975).

Note: in TSD, n =1, UF =100:

AEGL-2	0.40	0.20	0.050	0.025	30-exp (Drew et al.,1975).
AEGL-3	2.1 ppm	1.0 ppm	0.26	0.13	LC_{01} (Drew et al., 1975).

POTENTIAL ALTERNATE AEGL-3 VALUES FOR TECHNICAL GRADE CMME BASED ON BCME EXPOSURE

Scaling: $C^2 \times t = k$ (ten Berge et al., 1986)

Uncertainty factors: 10: 3 for intraspecies (among humans) variability
3 for interspecies (rat to human) variability

30 min	1 hr	4 hrs	8 hrs	Key Study/Endpoint
1.4	**0.97**	**0.48**	**0.34**	Kuschner et al., 1975. 1/41 rats given 10 exposures to 0.1 ppm BCME (6 h/day, 5 d/wk) developed a nasal adenocarcinoma; lifetime observation. **BCME⇒ 1.25 ppm CMME.**[1]
3.3	**2.3**	**1.2**	**0.82**	Drew et al., 1975. Rats and hamsters; 7-hour exp. to 0.7 ppm BCME caused life shortening; increased lung-to-body weight ratios, respiratory metaplasia and hyperplasia. **BCME⇒ 8.75 ppm CMME.**[1]

[1]AEGL values for CMME were obtained by calculating the amount of CMME that would contain that amount of BCME to which the animals were exposed (i.e. BCME conc. ÷ 0.08 ≈ CMME conc.)

Note: in TSD, n =1, UF =100: (additional modifying factor of 10 : 3 for variability in BCME content-***this should have been omitted***; 3 for potential carcinogenicity)

1.2	0.61	0.15	0.077	Kuschner et al., 1975. Rats: 0.1 ppm BCME
1.5	0.75	0.19	0.094	Drew et al., 1975. Rat 7-hr to 0.7 ppm BCME

POTENTIAL ALTERNATE AEGL-3 VALUES FOR TECH-CMME BASED ON EPA CARCINOGENICITY UNIT RISK FOR BCME (IRIS, 1998)

Key study: Kuschner et al., 1975. Male Sprague-Dawley rats given 10-100 six-hour, 0.1 ppm exposures (lifetime observation) had increased incidence of lung squamous cell carcinoma and nasal esthesioneuroepithelioma.

Inhalation Unit Risk -- **6.2E-2 per (ug/cu.m)**
Extrapolation Method -- Linerarized multistage procedure, extra risk
Air Concentrations at Specified Risk Levels:

1.6E-3 ug/cu.m	**E-4 (1 in 10,000)**
1.6E-4 ug/cu.m	E-5 (1 in 100,000)
1.6E-5 ug/cu.m	E-6 (1 in 1,000,000)

For 10^{-4} risk from lifetime (24-hour/day) exposure, total BCME exposure would be:
$(1.6 \times 10^{-3}\ \mu g/m^3)(25{,}600\ days) = \underline{40.96\ \mu g/m^3}$ **BCME**

Uncertainties re: stages of the carcinogenic process at which BCME acts, and because method was derived by COT for persons of young military age, an additional risk factor of 2.8 is applied: $40.96\ \mu g/m^3 \div 2.8 = \underline{14.63\ \mu g/m^3}$ **BCME**

$14.63\ \mu g/m^3$ **BCME** $\div 0.08 \Rightarrow \underline{183\ \mu g/m^3}$ **CMME** (0.0556 ppm CMME)
NOTE: ASSUMES CMME CARCINOGENICITY IS DUE SOLELY TO BCME

AEGL-3 Calculations:
24-hour exposure = 0.0556 ppm **CMME**; assuming linear (low-dose) extrapolation:

½-hour exposure = 0.0556 x 48 = **2.7 ppm**
1-hour exposure = 0.0556 x 24 = **1.4 ppm**
4-hour exposure = 0.0556 x 6 = **0.34 ppm**
8-hour exposure = 0.0556 x 3 = **0.17 ppm**

BCME (542-88-1) INFORMATION FROM THE IRIS (EPA) DATABASE

- Key study: Kuschner et al., 1975. Male Sprague-Dawley rats given 10-100 six-hour, 0.1 ppm exposures (lifetime observation) had increased incidence of respiratory tumors (neuroepitheliomas, malignant olfactory tumors (unclassified), ganglioneuroepitheliomas, squamous cell carcinomas of the turbinates and gingiva, poorly differentiated epithelial tumors of the nose, nasal cavity adenocarcinomas, and lung squamous cell carcinomas and adenocarcinomas. (Agency Work Group Review -- 07/23/86, 05/04/88; Verif. Date --05/04/88)

- There was a log-normal distribution of cancer induction time, with a median of 440 days. The cancer incidence shows a sigmoidal curve with time.

Number 0.1-ppm Exposures	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	0/240
10	0.000270	1/41
20	0.000541	3/46
40	0.00105	4/18
60	0.00184	4/18
80	0.00347	15/34
100	0.00373	12/20

- The human equivalent dose was calculated from the animal dose, assuming surface area equivalence. The animal dose was calculated from the air conc. (0.1 ppm or 0.479 mg/cu.m.), an assumed breathing rate (0.283 cu.m./day) for 500-g rats (assumed), and from the no. of exposures in each group. The 5/7 adjustment was not used; 483 days was the mean lifetime.

  $(0.479\ mg/m^3 \times 0.283\ m^3/d \times 6/24\ d) \div 0.5\ kg$ = **0.06778 mg/kg/day for rat**
  0.06778 mg/kg/day x 10 d/483 d = **0.001405 mg/kg/day for rat lifetime**
  $0.001383\ mg/kg/d \times (0.5/70)^{1/3}$ = **0.000271 mg/kg/day lifetime for humans**

- The unit risk should not be used if the air concentration exceeds 1.6E-1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

COMPARISON OF AEGL-3 VALUES (ppm) FOR TECHNICAL GRADE CMME OBTAINED BY VARIOUS APPROACHES							
30 m.	1 hr	4 hrs	8 hrs	n	UF	MF	Scenario (Reference)
1.8	1.3	0.65	0.46	2	10	3	Rat 7-hr **CMME** LC_{01} (Drew et al., 1975)
1.4	0.97	0.48	0.34	2	10	-	Rats; 10 x 0.1 ppm BCME 1/41 get respiratory cancer; **BCME⇒ CMME** (Kuschner et al., 1975)
3.3	2.3	1.2	0.82	2	10	-	Rat 7-hr to 0.7 ppm BCME;mortality; resp. metaplasia and hyperplasia. **BCME⇒ CMME** (Drew et al., 1975)
EPA (IRIS) unit risk for **BCME**: 6.2E-2 per (ug/m^3) based on Kuschner et al., 1975 **BCME⇒ CMME**							
2.7	1.4	0.34	0.17	1	-	-	10^{-4} risk: 1.6 x 10^{-3} ug/m^3 BCME
0.27	0.14	0.034	0.017	1	-	-	10^{-5} risk: 1.6 x 10^{-4} ug/m^3 BCME
0.027	0.014	0.0034	0.0017	1	-	-	10^{-6} risk: 1.6 x 10^{-5} ug/m^3 BCME

AEGL-2 VALUES FOR TECHNICAL GRADE CMME (Drew, et al., 1975)							
30'	**1 hr**	**4 hrs**	**8 hrs**	**n**	**UF**	**MF**	Rats; 30 six-hour 1 ppm t-**CMME**; held for life; 2/13 regenerative hyperplasia; 2/13 tracheobronchial squamous metaplasia; unexpl. death on d. 16, 22
0.12	0.082	0.041	0.029	2	10	3	

10^{-4} vs. 10^{-6} Risk for tech-CMME Carcinogenicity

Reasons for selecting 10^{-4} risk:

- No evidence for human carcinogenicity
- Lifetime or long-term exposure necessary to elicit CA
- Potent only at very high doses
- Neoplasia appears reversible (when discontinue treatment)
- Appears to be a "threshold" carcinogen

Reasons for selecting 10^{-6} risk:

- Proven human carcinogen
- Short time-to-tumor
- Evidence for cancer from a few exposures (in animals)
- Potent at low doses (0.1 ppm in rats)
- Complete carcinogen (BCME-yes for skin; CMME promoter only)
- Irreversible (when discontinue treatment)
- Mutagenic activity

Technical grade CMME response is more consistent with 10^{-6} risk.

Summary of Proposed AEGL Values for Dimethyldichlorosilane					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	18.5 ppm (98.1 mg/m^3)	13.1 ppm (69.4 mg/m^3)	6.55 ppm (34.7 mg/m^3)	4.63 ppm (24.5 mg/m^3)	Necrotic paws, corneal opacity, gray spots on lungs in rats (Dow Corning, 1997)
AEGL-3 (Lethality)	74.9 ppm (397 mg/m^3)	52.9 ppm (280 mg/m^3)	~~24~~ 26.5 ppm (~~130~~ mg/m^3)	18.7 ppm (99.1 mg/m^3)	1-hour rat LC_{01} (Dow Corning, 1997)

1/40

Attachment 9

- ONE MOLE OF DIMETHYLDICHLOROSILANE MAY REACT WITH WATER TO YIELD A MAXIMUM OF 2 MOLES OF HCL.

- LETHALITY DATA SUGGEST THAT DIMETHYLDICHLOROSILANE IS NOT AS TOXIC AS PREDICTED BY HCL MOLAR EQUIVALENTS. THIS IS LIKELY DUE TO INCOMPLETE HYDROLYSIS.

- THE EXACT MECHANISM OF ACTION IS UNKNOWN; HOWEVER, MUCH OF THE ACUTE TOXICITY IS LIKELY DUE TO HCL.

AEGL-1 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**NA**	**NA**	**NA**	**NA**

Insufficient data for derivation of AEGL-1 values

AEGL-2 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	18.5 [98.1]	13.1 [69.4]	6.55 [34.7]	4.63 [24.5]

Species: Rat
Concentration: 1309 ppm
Time: 1 hour
Endpoint: Necrotic paws, corneal opacity, gray spots on lungs
Reference: Dow Corning, 1997

n = 2

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between species)

Intraspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between individuals)

Modifying Factor = 3 x 3 = 10

Sparse data base = 3

Encroachment of values upon well-defined AEGL-3 = 3

Total UF and Modifying factors = 100

AEGL-3 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	74.9 [397]	52.9 [280]	24.5 [130]	18.7 [99.1]

Species: Rat
Concentration: 1589.5 ppm
Time: 1 hour
Endpoint: LC_{01}
Reference: Dow Corning, 1997

n = 2

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (mechanism is irritation and is not expected to vary greatly between species)

Intraspecies = 3 (mechanism is irritation and is not expected to vary greatly between individuals)

Modifying Factor = 3: Sparse data base

Total UF and Modifying factors = 30

Summary of Proposed AEGL Values for Dimethyldichlorosilane					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**NA**	**NA**	**NA**	**NA**	**NA**
AEGL-2 (Disabling)	**18.5 ppm (98.1 mg/m^3)**	**13.1 ppm (69.4 mg/m^3)**	**6.55 ppm (34.7 mg/m^3)**	**4.63 ppm (24.5 mg/m^3)**	**Necrotic paws, corneal opacity, gray spots on lungs in rats (Dow Corning, 1997)**
AEGL-3 (Lethality)	**74.9 ppm (397 mg/m^3)**	**52.9 ppm (280 mg/m^3)**	**24.5 ppm (130 mg/m^3)**	**18.7 ppm (99.1 mg/m^3)**	**1-hour rat LC_{01} (Dow Corning, 1997)**

ERPG, 1-hour (AIHA, 1989):

ERPG-1:	**0.8 ppm**
ERPG-2:	**5 ppm**
ERPG-3:	**25 ppm**

Summary of Proposed AEGL Values for Methyltrichlorosilane					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	8.79 ppm (53.6 mg/m^3)	6.22 ppm (37.9 mg/m^3)	3.11 ppm (18.9 mg/m^3)	2.20 ppm (13.4 mg/m^3)	Ocular opacity, irritation, and hunched posture in rats (Dow Corning, 1997)
AEGL-3 (Lethality)	39.79 ppm (242 mg/m^3)	28.13 ppm (172 mg/m^3)	14.07 ppm (85.8 mg/m^3)	9.95 ppm (60.7 mg/m^3)	1-hour rat LC_{01} (Dow Corning, 1997)

Attachment 10

- ONE MOLE OF METHYLTRICHLOROSILANE MAY REACT WITH WATER TO YIELD A MAXIMUM OF 3 MOLES OF HCL.

- LETHALITY DATA SUGGEST THAT METHYLTRICHLOROSILANE IS NOT AS TOXIC AS PREDICTED BY HCL MOLAR EQUIVALENTS. THIS IS LIKELY DUE TO INCOMPLETE HYDROLYSIS.

- THE EXACT MECHANISM OF ACTION IS UNKNOWN; HOWEVER, MUCH OF THE ACUTE TOXICITY IS LIKELY DUE TO HCL.

AEGL-1 FOR METHYLTRICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**NA**	**NA**	**NA**	**NA**

Insufficient data for derivation of AEGL-1 values

AEGL-2 FOR METHYLTRICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	8.79 [53.6]	6.22 [37.9]	3.11 [18.9]	2.20 [13.4]

Species: Rat
Concentration: 622 ppm
Time: 1 hour
Endpoint: Ocular opacity, irritation, and hunched posture
Reference: Dow Corning, 1997

n = 2

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between species)

Intraspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between individuals)

Modifying Factor = 3 x 3 = 10

Sparse data base = 3

Encroachment of values upon well-defined AEGL-3 = 3

Total UF and Modifying factors = 100

AEGL-3 FOR METHYLTRICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	39.79 [242]	28.13 [172]	14.07 [85.8]	9.95 [60.7]

Species: Rat
Concentration: 844 ppm
Time: 1 hour
Endpoint: LC_{01}
Reference: Dow Corning, 1997

n = 2

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (mechanism is irritation and is not expected to vary greatly between species)

Intraspecies = 3 (mechanism is irritation and is not expected to vary greatly between individuals)

Modifying Factor = 3: Sparse data base

Total UF and Modifying factors = 30

Summary of Proposed AEGL Values for Methyltrichlorosilane					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**NA**	**NA**	**NA**	**NA**	**NA**
AEGL-2 (Disabling)	**8.79 ppm (53.6 mg/m^3)**	**6.22 ppm (37.9 mg/m^3)**	**3.11 ppm (18.9 mg/m^3)**	**2.20 ppm (13.4 mg/m^3)**	**Ocular opacity, irritation, and hunched posture in rats (Dow Corning, 1997)**
AEGL-3 (Lethality)	**39.79 ppm (242 mg/m^3)**	**28.13 ppm (172 mg/m^3)**	**14.07 ppm (85.8 mg/m^3)**	**9.95 ppm (60.7 mg/m^3)**	**1-hour rat LC_{01} (Dow Corning, 1997)**

ERPG, 1-hour (AIHA, 1989):

ERPG-1: **0.5 ppm**
ERPG-2: **3 ppm**
ERPG-3: **15 ppm**

AEGLs For Epichlorohydrin

- Two cases of accidential high exposures caused liver and kidney damage.
- Occupational exposure have generally not been associated with any long-lasting effects.
- Epidemiologic studies in workers have generally been negative (expect for an increase in SMR for heart disease.)
- No increase in neoplastic diseases.
- Clastogenic effects in workers.

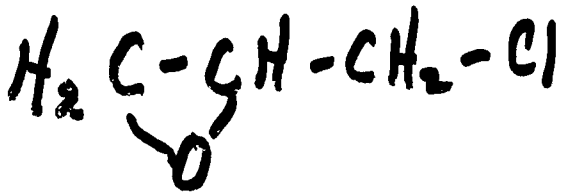
AEGLs For Epichlorohydrin

Epichlorohydrin is a colorless liquid at room temperature. It has a sweet, pungent, chloroform-like odor.

- Irritating to mucous membranes
- Odor recognition limit is about 25 ppp
- Causes respiratory, liver and kidney damage
- Mutagenic and carcinogenic in laboratory studies (Clastogenic in exposed workers)

AEGLs For Epichlorohydrin

Highly Reactive epoxide monomer used in the production of epoxy and phenoxy resins.



ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR EPICHLOROHYDRIN

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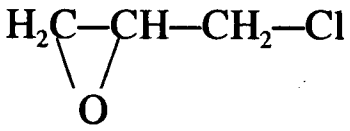
NAC/AEGL MEETING, WASHINGTON, D.C., MARCH 10-12, 1998

Attachment

Epichlorohydrin

Description	colorless liquid at room temperature; has a sweet, pungent or chloroform-like odor
Structural formula	
Synonym	2-(chloromethyl) oxirane
CAS Reg. No.	106-89-8
Chemical formula	C_3H_5ClO
Molecular weight	92.53
Vapor pressure	13 mm Hg@ 20°C
Max. sat. vap. conc.	17,100 ppm @ 20°C
Solubility	65.9 g/L of water @ 25°C
Conversion	1 ppm = 3.78 mg/m^3
Major uses	manufacture of epoxy and phenoxy resins, synthesis of glycerol
Producers	Shell Chemical Co. and Dow Chemical Co.

HUMAN DATA

- **Lethality data**: none found in the literature

- **Nonlethality data**:
  - **Odor threshold**: 0.08–12 ppm (AIHA, 1989)
    0.08 ppm for 18 subjects (Formin, 1966)
    10 ppm (Gardiner et al., 1993)
    10–12 ppm for 50% of subjects (Shell Oil Co., 1992)
    17 ppm (mean for 4 subjects) (UCC, 1983)
    25 ppm for 100% of subjects(Shell Oil Co., 1992)

  - **Other effects**: 0.08 ppm – electrical cerebral activity (Formin, 1966)

    17 ppm for 2 minutes – no effects
    68 ppm for 2 minutes – irritation to the pharynx
    136 ppm for 2 minutes – irritation to the eyes or pharynx (UCC, 1983)

    10–20 ppm – high enough to cause irritation (Enterline et al., 1990)
    20 ppm for 1 hour – burning to eyes and nose (Wexler, 1971)

    40 ppm – throat irritation lasting for 48 hours (Wexler, 1971)
    40 ppm for <2 hours – throat irritation (Deichmann and Gerarde, 1969)

HUMAN DATA (Continued)

- **Other effects**: 100 ppm – irritating to eyes and nose (Shell Oil Co., 1992)
  100 ppm – not tolerated because of pulmonary edema and kidney lesions (Wexler, 1971)
  > 100 ppm – marked nose and eye irritation (Gardiner et al., 1993)

- **Effects caused by exposure to high unknown concentrations**:

  Case study 1: **few breaths**: burning to eyes and nose, which increased intensity; delayed effects include swelling of face, malaise, vomiting, severe headache, shortness of breath, and feeling of suffocation; clinical examination showed mucous membrane inflammation, enlarged liver, jaundice; long-term consequence: chronic asthma-like bronchitis and liver disease (Schultz, 1964)

  Case study 2: **30 minute exposure**: delayed effects: burning to nose and throat, couth, chest gestion, runny nose, eye tenderness, headache, nausea;
  long-term consequence: more frequent upper respiratory tract infections, 40% increase in residual volume, and deceased arterial pO_2(NIOSH, 1976)

HUMAN DATA (Continued)

- **Carcinogenicity**: Human data are inadequate for evaluation

- **Developmental/Reproductive Toxicity** :
  Two epidemiologic studies showed no link to exposure to epichlorohydrin

- **Genetic Toxicity**: Positive evidence of clastogenicity (increased frequency of chromosomal aberrations) and increased frequency of sister chromatid exchanges (SCE) and cells with high frequency SCEs in workers exposed to epichlorohydrin at concentrations above 0.11 ppm; chromosomal aberrations decreased as exposure decreased from 0.26 to 0.10 ppm.

ANIMAL LETHALITY STUDY

- Study author: Dietz et al., 1985
- Study protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: Male and female Fischer 344 rats
  - Number: 6/group
  - Conc.: 552, 1008, 1097, or 3995 ppm (males and females); 2865 or 3275 ppm (males only) (TWA)
  - Duration: 1 hour
  - Observation: 14 days
  - Exp. conditions: dynamic, 2.6 m^3 stainless steel and glass Rochester-type inhalation chamber
  - Anal. methods: 7 times/hour by gas chromatography

- **Results:**
  - Mortality (time)

Conc. (ppm)	552	1008	1970	2865	3275	3995
Males	0/6	0/6	0/6	0/6	0/6	6/6 (days 1-4)
Females	0/6	0/6	2/6 (days 2 & 3)	-	-	6/6 (day 1)

LC_{50} - 3617 ppm (males determined by geometric mean of 3275 and 3995 ppm)
- 2165 ppm (females determined by moving average method)

ANIMAL LETHALITY STUDY

- Study author: Laskin et al., 1980
- Study Protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: Male Sprague-Dawley rats
  - Number: 20/group
  - Vapor conc.: 283, 303, 339, 369, 421, or 445 ppm
  - Duration: 6 hours (360 minutes)
  - Observation: 14 days
  - Exp. conditions: dynamic, 128 L or 1.3 m^3 inhalation chamber
  - Anal. method: every 30 minutes by spectrophotometry

- **Results:**
  - Mortality:
    LC_{50} = 360 ppm

283 ppm	303 ppm	339 ppm	369 ppm	421 ppm	445 ppm
0/20	1/20	1/20	15/20	16/20	17/20

  - Other effects: Signs of acute respiratory irritation with hemorrhage, severe edema of the lungs; elevated lung:body weight ratios at ≥339 ppm

ANIMAL LETHALITY STUDY

- Study author: UCC, 1983
- Study protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: Male Carworth Farm-Wistar rats
  - Number: 30 or 6/group, respectively
  - Vapor conc.: 580 or 1160 ppm
  - Duration: 4 hours (240 minutes)
  - Observation: 14 days
  - Exp. conditions: dynamic, 193 L hardboard inhalation chamber
  - Anal. methods: calculated from flow rate, and ratio of analytical to nominal concentrations determined from a repeat exposure study

- **Results:**
  - Mortality: 15/30 at 580 ppm and 6/6 at 1160 ppm
    LC_{50} = 182 ppm
  - Other effects: Irritation to mucous membranes, increased respiration, lethargy, and labored breathing; hemorrhagic lungs

ANIMAL LETHALITY STUDY

- Study author: UCC, 1983
- Study Protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: male mice, unspecified strain
  - Number: 6 or 11/group
  - Vapor conc.: 290, 580, or 1160 ppm
  - Duration: 4 hours (240 minutes)
  - Observation: 14 days
  - Exp. conditions: dynamic, 193 L hardboard inhalation chamber
  - Anal. methods: calculated from flow rate, and ratio of analytical to nominal concentrations determined from a repeat exposure study

- **Results:**
  - Mortality: 0/11 (290 ppm), 0/6 (580 ppm), 6/6 (1160 ppm)
    LC_{50} = 820 ppm
  - Other effects: irritation to mucous membranes, increased respiration, lethargy, and labored breathing (1160 ppm); irritation to mucous membranes (290 and 580 ppm)

ANIMAL LETHALITY STUDY

- Study author: UCC, 1983
- Study protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: Male guinea pigs, unspecified strain
  - Number: 4 or 6/group
  - Vapor conc.: 290, 580, or 1160 ppm
  - Duration: 4 hours (240 minutes)
  - Observation: 14 days
  - Exp. conditions: dynamic, 193 L hardboard inhalation chamber
  - Anal. methods: calculated from flow rate, and ratio of analytical to nominal concentrations determined from a repeat exposure study

- **Results:**
  - Mortality: 0/4 (290 ppm), 2/6 (580 ppm), 4/4 (1160 ppm)
    LC_{50} = 651 ppm
  - Other effects: irritation to mucous membranes, increased respiration, lethargy, and labored breathing in animals that died; irritation to mucous membranes in animals that survived

ANIMAL LETHALITY STUDY

- Study author: UCC, 1983
- Study protocol:
  - Test material: Epichlorohydrin vapor
  - Animals: Male rabbits
  - Number: 3/group
  - Vapor conc.: 290, 580, or 1160 ppm
  - Duration: 4 hours (240 minutes)
  - Observation: 14 days
  - Exp. conditions: dynamic, 193 L hardboard inhalation chamber
  - Anal. methods: calculated from flow rate, and ratio of analytical to nominal concentrations determined from a repeat exposure study.

- **Results:**
  - Mortality: 0/3 (290 ppm), 2/3 (580 ppm), 3/3 (1160 ppm)
    LC_{50} = 516 ppm
  - Other effects: Irritation to mucous membranes, increased respiration, lethargy, and labored breathing in animals that died; irritation to mucous membranes in animals that died.

Table 2. Summary of Acute Lethality Data in Various Animal Species

Species	Physical state	Exposure time	LC_{50} (ppm) (exp. range)	Other Effects	Reference
Rat	vapor	6 h	360	LC_{Lo} = 303 ppm (1/20); respiratory irritation and severe lung edema at ≥339 ppm	Laskin et al., 1980)
Rat	vapor	4 h	441 (290-580)	pulmonary irritation, but no deaths at 290 ppm; deaths at 580 ppm	UCC, 1983
Rat	vapor	4 h	580 (580-1160)	deaths at both conc.; irritation to mucous membranes (all animals) and lethargy, labored breathing, hemorrhagic lungs in nonsurvivors	UCC, 1983
Rat	vapor	4 h	635 (50-444)	toxicity in the liver, kidney, lungs, adrenals, thyroid (conc. not reported)	Grigorowa et al., 1974
Rat	vapor	1 h	2369 (552-3995)	LC_{LO} = 1970 ppm (2/12); nasal irritation, lacrimation, gasping, labored breathing, hyperactivity, lethargy, cyanosis, and/or weight loss at ≥1970 ppm	Dietz et al., 1985
Rat	vapor	5, 10, or 15 min	NA (23,400)	no deaths after 5 min; 5/6 after 10 min and 6/6 after 15 min; gasping in all groups; hemorrhagic lungs after 10 and 15 min	UCC, 1983
Mouse	vapor	6 hours	(687 = RC_{50})	All animals dead or moribund within 72 hours; moderate degeneration to nasal	Buckley et al., 1984

Table 2. Continued

Species	Physical State	Exposure Time	LC_{50} (ppm) (exp. range)	Other Effects	Reference
Mouse	Vapor	4 h	820 (290-1160)	deaths only at 1160 ppm; mucous membrane irritation all conc., lethargy and labored breathing at 1160 ppm	UCC, 1983
Mouse	vapor	4 h	1153 (132-2646)	LC_{lo} = 661 ppm (1/20); moderate mucous membrane irritation, and symptoms of toxicity (NOS) at ≥661 ppm	Mobay Chemical Corp., 1983
Mouse	vapor	2 h	794 (50-444)	toxicity in the liver, kidney, and lung (conc. not reported)	Grigorowa et al., 1974
Guinea pigs	Vapor	4 h	651 (290-1160)	LC_{lo} = 580 ppm (2/6); mucous membrane irritation all conc.; labored breathing and lethargy in nonsurvivors	UCC, 1983
Guinea pigs	vapor	4 h	275 (132-2646)	deaths and symptoms of toxicity (NOS) at ≥331 ppm; moderate to strong irritation ≥661 ppm	Mobay Chemical Corp., 1983
Rabbit	Vapor	4 h	516 (290-1160)	deaths at 580 (2/3) and 1160 ppm (3/3); mucous membrane irritation at all conc. labored breathing and lethargy in nonsurvivors	UCC, 1983

- Dietz et al., 1985
- **Nonlethal Effects – time of onset (minutes, hours, days): male/female rats combined** (*Mortality)

Conc. (ppm)	552	1008	1970*	2865	3275	3995*
Eye and nose pawing	–	–	–	–	–	2/2
Huddling and eyes shut	30/60	30/45	3/3	3	3	3/3
Shallow respiration	–	–	–	–	10	–
Gasping	–	–	30-108/66-108	30-68	30-50	28-54/28-52
Excessive salivation	–	–	150/138	–	–	–
Excessive nasal secretion	–	–	150/138	30-68	20-30	8/8
Hyperactivity	–	–	–	–	50	35-40
Cyanosis	–	–	–	–	–	45/52
Lacrimation	–	–	–	102	–	–
Excessive lacrimation	–	–	–	–	108	108/30-108
Bloody nasal secretion	–	–	–	–	–	108/108
Labored respiration	–	–	–	420	390	156/156
Porphyrin-like secretion	–	–	450/450	420	390	156-336/156
Lethargic	–	–	–	–	24 hours	336/336
Transient body weight loss	day 2	day 2	day 2	day 2	day 2-4	day 2
Diffuse visceral congestion	–	–	2/6 females	–	–	all animals
Corneal cloudiness, necropsy	–	–	1 male	5 males	6 males	–

Table 3. Clinical Signs, Mortality, and Time of Onset in Fischer 344 Rats Exposed by Inhalation to Epichlorohydrin for 6 Hours (Monsanto, 1983)

Clinical signs	Concentration (ppm)			
	10 & 25	50	100	200
Squinting	–	82 min	28 min	66 min
Hypoactivity	–	82 min	78 min	66 min
Head shaking	–	–	178 min	–
Drooping eyelids	–	–	223 min	126 min
Irritated eyes	–	–	–	136 min
Gasping	–	–	–	171 min
Red nasal discharge	–	–	–	266 min
Lacrimation	–	–	–	336 min
Mortality earliest	–	–	–	4/10 (day 4)

Table 4. Clinical Signs, Mortality, and Time of Onset in B6C3F$_1$ Mice by Inhalation to Epichlorohydrin for up to 6 Hours (Monsanto, 1983)

Clinical signs	Concentration (ppm)			
	10 & 25	50	100	200
Squinting	–	66 min	78 min	66 min
Hypoactivity	–	217 min	178 min	126 min
Drooping eyelids	–	–	223 min	126 min
Ruffed fur	–	–	–	306 min
Gasping	–	–	–	381 min
Mortality (earliest)	–	–	–	1/10 (day 6)

Table 5. Clinical Signs, Mortality, and Time of Onset in Syrian Hamsters by Inhalation to Epichlorohydrin for up to 6 Hours

Clinical signs	Concentration (ppm)				
	25	50	100	200	400
Salivation	-	82 min	268 min	126 min	-20 min
Hypoactivity	-	262 min	178 min	126 min	100 min
Squinting	-	-	78 min	66 min	60 min
Drooping eyelids	-	-	223 min	126 min	100 min
Excitation	-	-	-	216 min	40 min
Gasping	-	-	-	381 min	145 min
Full mouth pouches/saliva	-	-	-	306 min	240 min
Labored breathing	-	-	-	-	240 min
Mortality (earliest)	-	-	-	2/10 (day 7)	2/10 (day 3)

OTHER ANIMAL DATA

- Carcinogenicity: Male Sprague-Dawley rats exposed to 100 ppm, 6 hours/day, 5 days/week for 30 exposures observed for entire lifetime: nasal squamous cell carcinomas developed in 14/150; none in 150 controls.

  Male Sprague-Dawley rats exposed to 10 or 30 ppm, 6 hours/day, 5 days/week, for life: nasal squamous cell carcinoma developed in 1/100 at 30 ppm and no animals exposed to 10 ppm.

  Nonneoplastic lesions developed in the nasal cavity, larynx, trachea, lungs, and kidneys.

  Epichlorohydrin is clearly carcinogenic in rats; the neoplastic response to inhaled occurs only at the site of contact; a short-term intense exposure is more effective than long-term, low-level exposure.

- Genotoxicity: Mutagenic in bacteria, yeast, and mammalian cells in vitro. Inhalation of vapor results in chromosome aberrations in mouse bone marrow cells and spermatogonia at ≥ 1.3 ppm for 120 hours.

OTHER ANIMAL DATA (CONTINUED)

- Developmental/Reproductive Toxicity:

  No developmental effects at concentrations ≤25 ppm 7 hours/day during organogenesis in rats and rabbits

  Transient reduction in sperm motility in rats after exposure to 100 ppm for 4 hours

  Transient reduction in fertility in rats exposed to 25 or 50 ppm 6 hours/day, 5 days/week for 2–10 weeks

- Uptake and Metabolism:

  Exposure of rats to 1 and 100 ppm for 6 hours: percent uptake does not vary between; 72% of the dose excreted within 24 hours, most in urine followed by exhaled air; uptake rate was 15.48 and 1394 μg/hour, respectively, producing total doses of 0.37 and 33 mg/kg; six metabolites, but no epichlorohydrin, was excreted in urine; largest fraction taken up on nasal turbinates followed by lacrimal gland, large intestine, kidney, and liver.

Table 6. Nonlethal Effects in Animals Exposed to Epichlorohydrin by Inhalation			
Species	Exposure protocol	Effects	Reference
Rat	101–1963 ppm × 15 min	6–54% decrease in respiration; RC_{50} = 1342 ppm (50% ↓ in respiratory rate)	Gardner et al., 1985
Rat	100 ppm × 4 h	slight ↑ in kidney wt. in young rats; slight ↓ in BUN in young and adult rats; no microscopic evidence of liver or kidney damage	Robinson et al., 1995
Rat	1.9, 5.3, or 93 ppm × 4 h	↑ liver & kidney wt.; ↓lung and spleen wt.; ↑ urine protein & chlorides; ↓ spec. grav. & BSP removal from blood	Schumskaya et al., 1971
Rat	10 or 25 ppm × 6 h	no effect	Monsanto, 1983
Rat	50 or 100 ppm × 28–223 min	squinting, hypoactivity, head shaking, drooping eyelids	Monsanto, 1983
Rat	200 ppm × 136–336 min	same as 100 ppm plus irritated eyes, gasping, red nasal discharge, lacrimation	Monsanto, 1983
Rat	100 ppm × 7 h/d × 5 d/wk for 9 exposures	signs of nasal irritation after each exposure (discharge, sneezing, rubbing) after individual exposures; nasal epithelial and kidney degeneration after repeated exposures	Dow Chemical Co., 1982
Rat	150 ppm × 1 h or 5 ppm × 2 h/d × 6 d/wk for 20 exp.	severe kidney damage at 150 ppm; less severe at 5 ppm	Ito et al., 1995

Table 6. Continued

Species	Exposure protocol	Effects	Reference
Mouse	687 ppm × 10 min	RC_{50} (50% ↓ in respiratory rate)	Kane et al., 1979
Mouse	10 or 25 ppm × 6 h	no effect	Monsanto, 1983
Mouse	50, 100, or 200 ppm × 66–381 min	squinting, hypoactivity, drooping eyelids, ruffed fur, gasping	Monsanto, 1983
Mouse	100 ppm × 7 h/d × 5 d/wk for 9 exposures	signs of nasal irritation after each exposure (discharge, sneezing, rubbing) after individual exposures; nasal epithelial degeneration after repeated exposures	Dow Chemical Co., 1982
Mouse	5.3 ppm × 24 h	transient excitation, restlessness, sluggishness, somnolence	Formin, 1966
Hamster	25 ppm × 6 h	no effects	Monsanto, 1983
Hamster	50 or 100 ppm × 78–262 min	salivation, hypoactivity, squinting, drooping eyelids	Monsanto, 1983
Hamster	200 ppm × 66–381 min	same as 100 ppm plus excitation, gasping, full mouth pouch	Monsanto, 1983
Hamster	400 ppm × 20–240 min	same as 200 ppm plus labored breathing	Monsanto, 1983

Table 7. Estimates of Threshold for Lethality (LC_{01}) in Animals Exposed to Epichlorohydrin Vapor

Species	Exposure duration (minutes)	LC_{50} (ppm)	LC_{01} (ppm)	Reference
Rat	360	376	271 ± 13.7	Laskin et al., 1980
Rat	240	580	182 ±125	UCC, 1983
Rat	60	2369	721 ± 225	Dietz et al., 1985
Mouse	240	820	278 ± 100	UCC, 1983
Guinea pig	240	651	170 ± 115	UCC, 1983
Rabbit	240	516	100 ±112	UCC, 1983

ACUTE EXPOSURE GUIDELINES FOR EPICHLOROHYDRIN

AEGL -3 VALUES			
30 minutes	1 hour	4 hours	8 hours
471 ppm	**213 ppm**	**43 ppm**	**19 ppm**

Reference: Laskin et al., 1980

Test Species/Strain/Number: Male Sprague-Dawley rats, 20 per group

Exposure Route/Concentration/Durations: Inhalation, 283, 303, 339, 369, 421, or 445 ppm for 6 hours

Effects: Acute respiratory irritation, pulmonary hemorrhage and edema; elevated lung:body weight at ≥339 ppm
Mortality: 0, 1, 1, 15, 16, and 17, respectively

Endpoint/Concentration/Rationale: Lethality; LC_{01} = 271 ppm for a 6-hour exposure; the estimated threshold for lethality derived by probit analysis of the data.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, humans slightly more sensitive than animals (concentration up to 25 ppm for 7 hour without effect in animals, whereas 20 ppm for 1 hour causes burning of eyes and nose in humans).
Intraspecies: 3, effects due to exposure to concentrations above those which cause systemic effects may vary in the population because of differences in metabolism and excretion

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times t = k$, where n = 0.87 derived from empirical LC_{50} data for the rat exposed for 1, 4, or 8 hours

Confidence and Support of AEGL Values: The AEGL values for 30-minute and 1-hour exposures are probably too high, whereas those for 4- and 8-hour exposures are too low. Applying a total uncertainty factor of 30 ($10_A \times 3_H$) results in AEGL values that are too low across all exposure durations. AEGL-3 values will be reassessed after data from Dow Chemical Co. are obtained.

AEGL -2 VALUES			
30 minutes	1 hour	4 hours	8 hours
44 ppm	**20 ppm**	**20 ppm**	**20 ppm**

Reference: Wexler, 1971

Test Species/Strain/Number: Humans, number not reported

Exposure Route/Concentration/Durations: inhalation, 20 ppm for 1 hour

Effects: burning of eyes and nose

Endpoint/Concentration/Rationale: eye and nose irritation

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: not applicable
Intraspecies: 1, because all individuals are expected to respond similarly to eye and nose irritation

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: $C^n \times t = k$, where n = 0.87 derived from probit analysis of rat LC_{50} values for exposure durations of 1, 4, and 8 hours

Confidence and Support of AEGL Values: The AEGL values were flatlined at 20 ppm because applying the time scaling equation would yield 4- and 8-hour AEGL values that are below the OSHA PEL. These values for 30 minutes and 1 hour are supported by animal data in which exposure to 200 ppm for 136 minutes caused eye irritation; applying a total uncertainty factor of 30 ($10_A \times 3_H$) would yield AEGL values similar to those derived using the human data.

AEGL -1 VALUES			
30 minutes	1 hour	4 hours	8 hours
10 ppm	**10 ppm**	**10 ppm**	**10 ppm**

Reference: Shell Oil Co., 1992

Test Species/Strain/Number: Humans, number not reported

Exposure Route/Concentration/Durations: Inhalation, 10–12, 25, or 100 ppm for 5 minutes

Effects: 0–12 ppm, odor threshold for 50% of subjects; 25 ppm odor threshold for 100% of subjects; 100 ppm, eye and nose irritation

Endpoint/Concentration/Rationale: odor threshold for 50% of subjects, 10 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: not applicable
Intraspecies: 1, because a concentration of 10 ppm would be detected by most individuals

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: not applicable

Confidence and Support of AEGL Values: Other reports stated that the odor threshold for epichlorohydrin was below 1 ppm, however, Shell Oil Co. (1992) reported that exposure to epichlorohydrin concentrations at the OSHA PEL are not detectable by odor, and other means of monitoring were required to assure that workplace air concentrations are below 5 ppm.

$Ni(CO)_4$

MP ~ -20°C

BP 43°C

FP <20°C

AIT EXPLODES ABOVE 60°C.

DECOMPOSES IN AIR

50% @ ROOM TEMP

100% @ 150-200°C

$Ni(CO)_4$

Reported Kinetics

$$Ni(CO)_4 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ni(CO)_3 + CO$$

$$Ni(CO)_3 + O_2 \xrightarrow{k_3} Ni(CO)O + CO + CO_2$$

$$\uparrow = \frac{1}{k_1} + \frac{k_2 [CO]}{k_1 k_3 [O_2]}$$

$\uparrow$ = 1 minute @ 0 ppm CO

$\uparrow \cong$ 1 min + 0.5 min x [CO]

AEGL DEVELOPMENT
for
NICKEL CARBONYL

NAC/AEGL Meeting 9
March 10-12,1998

Old Post Office, M09
1100 Pennsylvania Ave., N.W.
Washington, D.C.

ORNL Staff Scientist:
Robert A.Young
Chemical Manager:
Kyle Blackman
Chemical Reviewers:
Zarena Post
Glenn Leach

AEGL-1

- Quantitative data unavailable
- Odor threshold: 0.5 - 3.0 ppm
- Adverse effects at or below odor detection
- Human volunteers exposed to "whiffs" of 0-5 ppm (Sunderman 1990)
  - recognition responses erratic
  - no exposure duration provided
- AEGL-1 not recommended

AEGL-2

- **Quantitative data in humans unavailable**

- **Animal data**
  - **developmental toxicity in rats and hamsters**

AEGL-3

- **Quantitative data in humans limited**

- **Animal data**
  - **lethality data (LC_{50}) for four species**
  - **sensitivity inversely proportional to body mass**

- **Mouse most sensitive**

- **Data unavailable for calculating *n* for $C^n \times t = k$; default to $n = 2$**

- **Uncertainty factors**
  - **10 for intraspecies variability**
  - **10 for interspecies variability**

ACUTE LETHALITY OF NICKEL CARBONYL IN HUMANS	
Acute lethality value	**Reference**
30-min LC_{50}: 3 ppm (estimated)	**Kincaid et al., 1956**
30 ppm: immediately fatal (estimated)	**Vuopola et al., 1970**

ACUTE LETHALITY OF NICKEL CARBONYL IN ANIMAL SPECIES		
Species	**Acute lethality value**	**Reference**
Rat	30-min LC_{50}: 56 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Rat	30-min LC_{50}: 33.6 ppm	Kincaid et al., 1953
Rat	30-min LC_{75}: 80 ppm	Sunderman and Donnelly,1965
Rat	15-min LC_{50}: 81.2 ppm	Baselt et al., 1977
Mouse	30-min LC_{50}: 9.38 ppm	Kincaid et al., 1953
Rabbit	30 min LC_{50}: 42-168 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Cat	30-min LC_{50}: ≈266 ppm[b]	Kincaid et al., 1953

[a] 50% mortality value determined by Kincaid et al. (1953) using probit analysis and multiple exposure time data of Barnes and Denz (1951).

[b] value estimated by authors based upon 100% (3/3) mortality at 280 ppm for 30 minutes but no mortality (0/2) at 271.6 ppm for 30 minutes.

MALFORMATIONS IN RATS FOLLOWING 15-MINUTE GESTATIONAL EXPOSURE TO NICKEL CARBONYL DURING GESTATION							
Observation	**Group A**	**Group B**	**Group C**	**Group D**	**Group E**	**Group F**	**Group G**
Exposure (mg/L)	**sham**	**CO**	**0.16**	**0.30[a]**	**0.08**	**0.16**	**0.16**
Exposure day	**8**	**7**	**7**	**7**	**8**	**8**	**9**
Live fetuses/litter	**9.2±2.1**	**8.3±2.6**	**8.1±2.6**	**9.1±1.6**	**7.6±3.6**	**8.3±2.6**	**7.4±4.8**
Live fetuses/ conceptuses	**110/114**	**187/215‡**	**113/135‡**	**91/100†**	**121/134†**	**108/120†**	**96/112†**
Mean fetus wt. (g)	**3.4±0.2**	**3.1±0.7**	**3.0±0.3‡**	**3.0±0.4‡**	**3.3±0.5**	**3.1±0.3‡**	**3.2±0.3‡**
Litters with malformed fetuses	**0/12**	**0/22**	**9/14***	**9/10***	**2/16**	**9/13***	**0/13**
Total malformations[b]	**0**	**0**	**15***	**29***	**2**	**19***	**0**

[a] **Only 10 of 19 dams lived to day 20**

[b] **Ocular malformations: bilateral anophthalmia, unilateral anophthalmia, bilateral microphthalmia, unilateral microphthalmia, anophthalmia and microphthalmia; only one incidence each in the Group C and Group D was categorized as other than ophthalmic anomalies. † $p<0.05$; ‡ $p<0.01$; * $p<0.001$**

TERATOGENIC EFFECTS OF NICKEL CARBONYL INHALATION (8.4 ppm, 15 min/day) IN PREGNANT SYRIAN HAMSTERS		
Parameter	**Control**	**$Ni(CO)_4$-treated**
Total malformations[a]	**0% (0/9)**	
day 4 exposure		**5.5% (8/146)***
day 5 exposure		**5.8% (10/171)***
Proportion of litters with malformed fetuses	**0% (0/9)**	
day 4 exposure		**33% (4/12)***
day 5 exposure		**24% (4/17)***
Serous cavity hemorrhage	**0% (0/9)**	
day 4 exposure		**18% (26/146)***
day 5 exposure		**25% (42/171)***

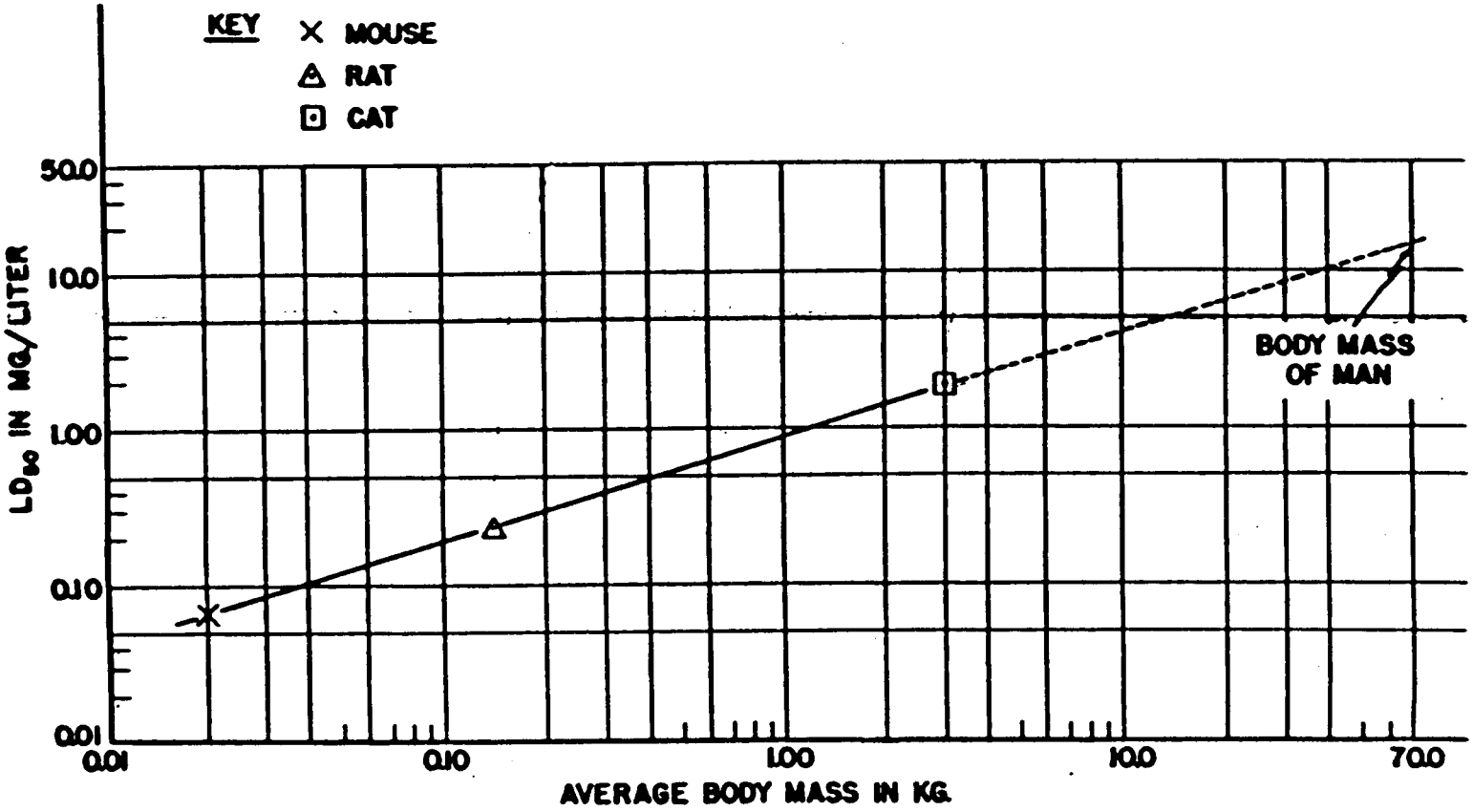
a **Included 9 fetuses with cystic lungs, 7 fetuses with exencephaly, 1 fetus with exencephaly plus fused rib, and 1 fetus with anophthalmia plus cleft palate; for fetuses of dams exposed on days 6 or 7, there was 1 fetus with fused ribs and 2 fetuses with hydronephrosis.**

* **Significantly different from controls ($p<0.05$)**

PROPOSED AEGL VALUES FOR NICKEL CARBONYL (ppm [mg/m^3])					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	**NA**	**NA**	**NA**	**NA**	**not appropriate; toxicity may occur in the absence of detection**
AEGL-2	**NA**	**NA**	**NA**	**NA**	**not appropriate; date are insufficient to determine a reliable estimate for AEGL-2 values**
AEGL-3	**0.03 [0.22 mg/m^3]**	**0.02 [0.15 mg/m^3]**	**0.01 [0.08 mg/m^3]**	**0.008 [0.05 mg/m^3]**	**estimated lethality threshold using mouse lethality data of Kincaid et al., (1953)**

ISSUES

- **Data deficiencies for AEGL-1**
- **Data deficiencies for AEGL-2**
- **Uncertainty factor application**
  - **UF of 3 for interspecies variability**
    - **body mass - toxicity relationship**
    - **epidemiologic studies (long-term exposure to 0.072 ppm - not life threatening)**



Relationship between the L.D.$_{50}$ and the size of three experimental animals.

Kincaid et al., 1953

Effect of Uncertainty Factor Adjustment on AEGL-3 Values for Nickel Carbonyl

Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-3					estimated lethality threshold (3.17 ppm; n = 2) using mouse lethality data of Kincaid et al., (1953)
	0.03	0.02	0.01	0.008	UF = 100: 10 for interspecies; 10 for intraspecies
	0.11	0.07	0.04	0.03	UF = 30: 3 for interspecies; 10 for intraspecies
	0.32	0.22	0.11	0.08	UF = 10: 3 for interspecies; 3 for intraspecies

ACUTE EXPOSURE GUIDELINES FOR NICKEL CARBONYL
(CAS NO. 13463-39-3)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
NA	NA	NA	NA

Reference: Sunderman (1990)

Test Species/Strain/Number: human volunteers, six subjects (age and gender not specified)

Exposure Route/Concentrations/Durations: "whiffs" of 0-5 ppm; duration not specified

Toxicity Endpoint: ability to detect exposure was erratic

Time Scaling: not relevant

Concentration/Time Selection/Rationale: not relevant

Uncertainty Factors/Rationale
Total Uncertainty Factor: not relevant

Modifying Factor: not relevant

Animal-to-Human Dosimetric Adjustments: none; human subjects

Comments: Because of the difficulty in detecting exposure concentrations that may result in a toxic response and the lack of both human and animal data consistent with AEGL-1 effects, an AEGL-1 is considered to be inappropriate

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 8 Highlights
Disabled American Veterans Building
807 Maine Avenue
Washington, D.C.
December 8-10, 1997

INTRODUCTION

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 7 (September 23-25, 1997) were reviewed and approved (Appendix A).

Dr. Roger Garrett reported that comments had been received on the AEGLs published in the Federal Register and that the public comment period was closed. He also stated that there had been a meeting with the National Academy of Sciences (NAS) Committee on Toxicology (COT) and that arrangements are in progress for COT review of Interim AEGL values.

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group
A report from the SOP Working Group was given by Ernest Falke. An overview of the first three chapters (Calculations of AEGL Values, Format and Content of Technical Support Documents, Development of Information and Data for Technical Support Documents [TSD]) was provided. Topics for which work is currently in progress include AEGL endpoints (e.g., types of endpoints, categorization of endpoints and their relationship to AEGL levels) and time scaling (e.g., how concentration-time relationship varies with endpoint, concentration range, or time frame; derivation of *n* and relevant statistics). Additional issues were mentioned that should also be addressed in the SOP and they include: contact and use of manufacturers' information, sharing of draft TSD with chemical manufacturers prior to the NAC/AEGL meetings, review procedures (i.e., TSD review, Federal Register comment period, COT process), and refinement of definitions (e.g., "ceiling level," "notable discomfort").

Action Item: Provide comments on SOP to Ernest Falke ASAP. He would like to have a revised SOP by 1/1/98.

Deriving AEGLs by Bench Dose Approach
Bob Benson and Bob Snyder volunteered to do this and will report their results in the next NAC meeting.

Federal Register Comments on Proposed Draft AEGLs
Roger Garrett and Rich Neimeier presented a brief overview of the public comments on the

Proposed AEGLs published in the Federal Register (Vol. 62, No. 210, pp. 58840-58851). Both chemical-specific and general comments were received and provided by the Federal Register office. They were reviewed first time during the meeting. A total of ten parties provided comments as of that date.

Richard Thomas and Ernie Falke will discuss the human equivalence adjustment for hydrazine.

A motion was made (Mark McClanahan), seconded (Loren Koller), and approved that the following AEGLs be considered as Interim AEGLs and that they be forwarded to the COT: 1,1-dimethylhydrazine, 1,2,-dimethylhydrazine, methylhydrazine, aniline, 1,2-dichloroethylene, nitric acid, fluorine, and arsine.

American Chemical Society (ACS) Presentations

Nancy Kim, George Rodgers and Robert Young presented abbreviated versions of their talks originally presented at the American Chemical Society meeting in Las Vegas (September 1997). These presentations were part of the Chemical Health and Safety Division symposium entitled "National Program for the Development and Use of Acute Exposure Guideline Levels" organized by Po-Yung Lu, Paul Tobin, and Roger Garrett. Nancy Kim spoke about the tracking of accidental releases in the state of New York and the application of AEGLs. George Rodgers presented information pertaining to sensitive populations, pertinent factors to consider in this respect for the development of AEGLs, and examples of sensitive responders. Robert Young provided an overview of the development of Technical Support Documents and some of the thought processes relevant to data evaluation and derivation of draft proposed AEGLs.

AEGL PRIORITY CHEMICALS

Phosgene, CAS No. 75-44-5

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Cheryl Bast, ORNL

Cheryl Bast provided an overview of the work on the phosgene draft AEGLs and the most recent adjustment to these values (Attachment 3). T. D. Landry (Dow Chemical), representing the Chemical Manufacturers Association (CMA) Phosgene Panel, stated that the CMA supported the values but considered the use of Haber's Rule (linear extrapolation) for 4-hour and 8-hour AEGLs to result in somewhat conservative, but appropriately protective, values (Attachment 4). Dr. Werner Diller (also representing the CMA Phosgene Panel) provided positive comments on the phosgene TSD and the AEGL endpoints (Attachment 5), but remarked that he had reservations regarding the "Not Applicable" status for AEGL-1 and the use of animal data to derive the AEGLs. He indicated that the proposed draft AEGLs were somewhat low (due to interspecies uncertainty factor application) and that they did not necessarily reflect the human experience. Discussion followed regarding the relationship between the AEGL values and the TLV, and the application of a benchmark dose approach for evaluating the data. A motion was made (Loren Koller) and seconded

(George Rodgers) to accept the proposed draft AEGLs for phosgene. The motion passed (YES:23; NO:0; ABSTAIN:0; ABSENT:9) (Appendix B). The proposed AEGLs for phosgene are shown in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSGENE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.60 ppm (2.5 mg/m^3)	0.30 ppm (1.2 mg/m^3)	0.08 ppm (0.33 mg/m^3)	0.04 ppm (0.16 mg/m^3)	chemical pneumonia in rats (Gross et al., 1965)
AEGL-3	1.5 ppm (6.2 mg/m^3)	0.75 ppm (3.1 mg/m^3)	0.20 ppm (0.82 mg/m^3)	0.09 ppm (0.34 mg/m^3)	30-min no effect level for lethality in rats (Zwart et al., 1990)

Hydrogen Cyanide, CAS No. 74-90-8

Chemical Manager: Dr. George Rodgers, AAPCC
Author: Dr. Sylvia Talmage, ORNL

George Rodgers presented an overview of cyanide toxicology and metabolism, and briefly discussed populations at risk. Overall, the toxic response to cyanide is similar across species with sensitivity variances being due primarily to variable levels of rhodanese. The AEGL values presented in the draft TSD appeared to be consistent with occupational standards and criteria, and the available acute toxicity data for this chemical. The draft AEGLs in the TSD were derived using a total uncertainty factor of 6 (3 for intraspecies variability and 2 for interspecies variability). A discussion on the interspecies uncertainty factor followed. George Rodgers moved that the AEGL values as originally proposed in the TSD be accepted with the following modifications: change the interspecies uncertainty factor to 1 and add a modifying factor of 2. Loren Koller seconded the motion which carried (YES:24; NO:1; ABSTAIN:0; ABSENT:8) (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CYANIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	toxicity below odor threshold
AEGL-2	10 ppm (11 mg/m3)	7 ppm (7.8 mg/m3)	3.5 ppm (3.9 mg/m3)	2.5 ppm (2.8 mg/m3)	slight central nervous system depression (Purser, 1984)
AEGL-3	21 ppm (23 mg/m3)	15 ppm (17 mg/m3)	8.6 ppm (9.7 mg/m3)	6.6 ppm (7.3 mg/m3)	lethality (LC_{01}) in rats (E.I. duPont de Nemours, 1981)

Carbon Tetrachloride, CAS No. 56-23-5

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Robert Young, ORNL

Robert Young presented the data sets pertinent to derivation of AEGLs for carbon tetrachloride and the draft proposed AEGLs (Attachment 6). The draft proposed AEGL-1 and AEGL-2 values were based upon human data. It was also the consensus of the NAC/AEGL to use these data for AEGL-1 and AEGL-2 values. Several LC_{50} data sets from animals were available to derive AEGL-3 values. Following discussion of the various data set elements, the values in the following table were proposed and approved by the NAC/AEGL. The AEGL-1 values were derived from controlled human exposures (Davis, 1934) in which subjects experienced nervousness and slight nausea following 30-minute exposure to 158 ppm. A motion to accept the AEGL-1 values was made by Richard Thomas and seconded by Tom Sobotka. The motion passed unanimously (YES: 24; NO: 0; ABSTAIN: 0; ABSENT: 8). Additional data from Davis supported the AEGL-1 values. Similarly, human data from controlled exposures (Davis, 1934) were used to derive the AEGL-2 values. These were based upon nausea, headache, and vomiting resulting from a 15-minute exposure to 1,191 ppm; one of four subjects found this exposure to be intolerable. A motion to accept the AEGL-2 values was made by Bill Benson and seconded by Bill Bress. The motion passed (YES:18; NO:6; ABSTAIN:0; ABSENT:8). Both the AEGL-1 and AEGL-2 values used a total uncertainty factor of 10 for protection of sensitive individuals (e.g., consumers of alcohol or those exposed to cytochrome P-450 inducers), and temporal extrapolation $C^n \times t = k$, where n = 2.5 based upon animal lethality data. The AEGL-3 values were based upon an estimated lethality threshold (LC_{01}) derived from rat lethality data. A total uncertainty factor of 30 was applied; 10 for protection of sensitive individuals and 3 for interspecies variability (subchronic animal studies showed that long-term exposures at or above the proposed AEGL-3 values did not result in lethal responses). Temporal extrapolation used $C^n \times t = k$, where n = 2.5 based upon animal lethality data. Because there was uncertainty regarding the possibility of delayed hepatotoxic effects, it was suggested that mention be made of antioxidant treatment for exposures to AEGL-2 or AEGL-3 levels. A motion to accept the AEGL-3 values was made by Bill Bress and seconded by Larry Gephart. The motion passed (YES:21; NO:1; ABSTAIN:0; ABSENT:10) (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	16 ppm (100.6 mg/m^3)	12 ppm (75.5 mg/m^3)	6.9 ppm (43.4 mg/m^3)	5.2 ppm (32.7 mg/m^3)	nervousness, slight nausea in human subjects (Davis, 1934)
AEGL-2	90 ppm (566.1 mg/m^3)	68 ppm (427.7 mg/m^3)	39 ppm (245.3 mg/m^3)	30 ppm (188.7 mg/m^3)	nausea, vomiting, headache in human subjects (intolerable to one of four subjects) (Davis, 1934)
AEGL-3	230 ppm (1,446.7 mg/m^3)	170 ppm (1,069.3 mg/m^3)	99 ppm (622.7 mg/m^3)	75 ppm (471.8 mg/m^3)	estimated lethality threshold (LC_{01} = 5,135.5 ppm) in rats (Adams et al.,1952; EPA-OTS, 1986)

Trimethylchlorosilane, CAS No. 75-774
Methyltrichlorosilane, CAS No. 75-79-6

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL

An overview of the information available for these chemicals was presented by Cheryl Bast. Dr. Robert Meeks (representing SEHSC) also provided information regarding current research on some of the chlorosilanes and the difficulties inherent to research on this class of chemicals. Fundamental questions/issues regarding these chemicals include hydrolysis rate and the effect of environmental conditions on the reactivity of these chemicals. Due to the paucity of data on these chemicals and uncertainties regarding the identification of the hydrolysis products and the fate of the silicone moiety, it was the consensus of the NAC/AEGL to defer deliberations pending receipt and incorporation of industry data.

Arsenic Trichloride, CAS No. 7784-34-1

Chemical Manager: Dr. William Bress, ASTHO
Author: Dr. Robert Young, ORNL

By way of introduction, Bill Bress explained that data pertinent to AEGL derivation were extremely limited for this chemical but that it was being brought before the NAC/AEGL to introduce an elemental equivalent methodology. Robert Young explained that the only data available for the title chemical were unverifiable lethality data from early reports (Attachment 7). These reports lacked experimental details and provided no information on analytical techniques. Although draft proposed AEGL-3 values were provided in the technical support document, Robert Young explained that the data were not considered to be appropriate for derivation of AEGL-3 values for the aforementioned reasons. No additional toxicity data were available for arsenic trichloride and no AEGL-1 values were proposed. Limited data pertinent to AEGL-2, were available for another trivalent arsenical, arsenic trioxide. For AEGL-2, an elemental equivalence approach was introduced whereby an arsenic trichloride exposure is based upon an elemental arsenic equivalence to arsenic trioxide. Robert Young explained that although this approach has been used for Reference Doses, Reference Concentrations and Reportable Quantity values, it did not appear to be scientifically defensible for application to deriving AEGLs for arsenic trichloride. The critical factors driving this judgement included: (1) validity of assuming the arsenic moiety to be the determinant of acute toxicity, (2) differences in physicochemical properties of the two arsenicals, and (3) dramatically different toxic potency of the two arsenicals. It was noted by Robert Young that the decision to recant this approach was attained through discussion among the ORNL staff scientist, the chemical manager, and chemical reviewers (Thomas Hornshaw and Steven Barbee). Although the methodology was considered inappropriate for arsenic trichloride, it is an approach that may be considered in the future where chemical-specific data are unavailable or limited. George Rodgers moved and Ernest Falke seconded that AEGLs not be derived for arsenic trichloride and that an effort be made to determine its inclusion as an AEGL priority chemical. The motion passed unanimously.

Sulfur Dioxide, Sulfur Trioxide, Sulfuric Acid Review

Cheryl Bast presented an overview of currently available data on sulfur dioxide, sulfur trioxide and sulfuric acid.

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

March 10-12, 1998 (at Oak Ridge ??)
June 15-17, 1998
September 14-16, 1998
December 7-9, 1998

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC/AEGL Meeting No. 8 Agenda
2. NAC/AEGL Meeting No. 8 Attendee List
3. Data analysis of Phosgene - Cheryl Bast
4. Data analysis of Phosgene - T.D. Landry
5. Data analysis of Phosgene - Werner Diller
6. Data analysis of Carbontetrachloride - Bob Young
7. Data analysis of Arsenic trichloride - Bob Young

LIST OF APPENDICES

A. Approved NAC/AEGL-7 Meeting Highlights
B. Ballot for Phosgene
C. Ballot for Hydrogen cyanide
D. Ballot for Carbontetrachloride

Date of AEGL NAC meeting: 3/11/98 **Chemical:** METHYLHYDRAZINE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A		
Steven Barbee	N		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	A		
Kyle Blackman	Y		
Jonathan Borak	Y		
William Bress	A		
Luz Claudio	A		
George Cushmac	Y		
Ernest Falke	Y		
Larry Gephart	Y		
John Hinz	Y		
Jim Holler	Y		
Thomas C. Hornshaw	Y		
Nancy K. Kim	A		

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y		
Glenn Leach	Y		
Mark A. McClanahan	Y		
John S. Morawetz	Y		
Richard W. Niemeier	Y		
William Pepelko	Y		
Zarena Post	A		
George Rodgers	Y		
George Rusch, Chair	Y		
Bob Snyder	A		
Thomas J. Sobotka	Y		
Kenneth Still	Y		
Patricia Ann Talcott	A		
Richard Thomas	Y		
Thomas Tuccinardi/ Doan Hansen	A Y		
BEN JACKSON	A		
TALLY	22/23	22/23	22/23

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	5.2 ,( )	2.2 ,( )	0.41 ,( )	0.18 ,( )
AEGL 3	25 ,( )	11 ,( )	2.0 ,( )	0.86 ,( )

* Based on n = 0.82 instead of n = 1

AEGL 1 Motion: G. RODGERS **Second:** E. FALKE

AEGL 2 Motion: " **Second:** "

AEGL 3 Motion: " **Second:** "

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/11/98

CAS# 107-30-2

Date of AEGL NAC meeting: 3/10/98 **Chemical:** CHLOROMETHYL METHYL ETHER

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	A	A	A
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	A	A	A
Luz Claudio	A	A	A
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	N	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	N	Y
Nancy K. Kim	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	Y	Y	Y
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	Y	Y	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
BEN JACKSON	A	A	A
TALLY	23/23	21/23	23/23

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	0.12 ,( )	0.082,( )	0.041 ,( )	0.029 ,( )
AEGL 3	1.8 ,( )	1.3 ,( )	0.65 ,( )	0.46 ,( )

AEGL 1 Motion: George Rodgers **Second:** Loren Koller

" "

AEGL 2 Motion: _____ **Second:** _____

" "

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 3/10/98

75-78-5

Date of AEGL NAC meeting: 3/12/98 **Chemical:** DICHLORODIMETHYLSILANE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A	A	A	Loren Koller	A	A	A
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	A	A	A	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	Y	Y	Y
Robert Benson	A	A	A	Richard W. Niemeier	Y	Y	Y
Kyle Blackman	Y	Y	Y	William Pepelko	Y	Y	Y
Jonathan Borak	A	A	A	Zarena Post	A	A	A
William Bress	A	A	A	George Rodgers	Y	Y	Y
Luz Claudio	A	A	A	George Rusch, Chair	Y	Y	Y
George Cushmac	Y	Y	X	Bob Snyder	A	A	A
Ernest Falke	Y	Y	Y	Thomas J. Sobotka	A	A	A
Larry Gephart	Y	Y	Y	Kenneth Still	A	A	A
John Hinz	Y	Y	Y	Patricia Ann Talcott	A	A	A
Jim Holler	Y	Y	Y	Richard Thomas	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
Nancy K. Kim	A	A	A	Ben Jackson	A	A	A
				TALLY	17/17	17/17	17/17

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.9 ,( )	0.9 ,( )	0.9 ,( )	0.9 ,( )
AEGL 2	26 ,( )	13 ,( )	3.3 ,( )	1.6 ,( )
AEGL 3	106 ,( )	53 ,( )	13 ,( )	6.6 ,( )

AEGL 1 Motion: D. Belluck **Second:** T. Hornshaw

AEGL 2 Motion: G. Rodgers **Second:** D. Belluck

AEGL 3 Motion: T. Hornshaw **Second:** D. Belluck

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/12/98

75-79-6

Date of AEGL NAC meeting: **Chemical:** TRICHLOROMETHYL SILANE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	P	P	P
David Belluck	Y	Y	Y
Robert Benson	A	A	A
Kyle Blackman	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	A	A	A
Luz Claudio	A	A	A
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy K. Kim	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	A	A	A
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	Y	Y	Y
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	A	A	A
Kenneth Still	A	A	A
Patricia Ann Talcott	A	A	A
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A ● Y ●
Ben Jackson	A	A	A ●
TALLY	17/17	17/17	17/17

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.6 ,( )	0.6 ,( )	0.6 ,( )	0.6 ,( )
AEGL 2	12 ,( )	6.2 ,( )	1.6 ,( )	0.7 ,( )
AEGL 3	56 ,( )	28 ,( )	7.0 ,( )	3.5 ,( )

AEGL 1 Motion: Hornshaw **Second:** Barbee

AEGL 2 Motion: Rodgers **Second:** R. Niemeier

AEGL 3 Motion: G. Rodgers **Second:** S. Barbee

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 3/12/98

Date of AEGL NAC meeting: 3/11/98 **Chemical:** EPICHLOROHYDRIN

NAC Member	AEGL 1	AEGL 2	AEGL 3	
George Alexeeff	A	A	A	A
Steven Barbee	Y	Y	Y	Y
Lynn Beasley	Y	Y	Y	Y
David Belluck	Y	Y	Y	P
Robert Benson	A	A	A	A
Kyle Blackman	Y	Y	Y	Y
Jonathan Borak	Y	A	Y	A
William Bress	A	A	A	A
Luz Claudio	A	A	A	A
George Cushmac	Y	Y	Y	Y
Ernest Falke	Y	Y	Y	Y
Larry Gephart	Y	Y	P	P
John Hinz	Y	Y	P	P
Jim Holler	Y	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y	Y
Nancy K. Kim	A	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL3	
Loren Koller	Y	A	A	A
Glenn Leach	Y	Y	Y	Y
Mark A. McClanahan	Y	N	N	N
John S. Morawetz	Y	Y	Y	P
Richard W. Niemeier	Y	Y	Y	Y
William Pepelko	Y	A	Y	Y
Zarena Post	A	A	A	A
George Rodgers	Y	Y	Y	Y
George Rusch, Chair	Y	Y	Y	Y
Bob Snyder	A	A	A	A
Thomas J. Sobotka	Y	N	Y	Y
Kenneth Still	Y	Y	Y	Y
Patricia Ann Talcott	A	A	A	A
Richard Thomas	A	A	A	A
Thomas Tuccinardi/ Doan Hansen	A N	A P	A N	A P
BEN JACKSON	A	A	A	A
TALLY	21/22	16/18	12/19	

1 PASS

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	5 ,( )	5 ,( )	5 ,( )	5 ,( )
AEGL 2	[redacted] 33 ,( )	[redacted] 24 ,( )	[redacted] 16 ,( )	[redacted] 10 ,( )
AEGL 3	160 ,( )	72 ,( )	43 ,( )	*30 ,( )

AEGL 1 Motion: L. GEPHART **Second:** L. KOLLER

AEGL 2 Motion: S. BARBEE **Second:** J. HINZ

AEGL 3 Motion: J. BORAK **Second:** D. BELLUCK

Approved by Chair: [signature] **DFO:** [signature] **Date:** 3/11/98

Date of AEGL NAC meeting: **Chemical:** NICKEL CARBONYL

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff			A	Loren Koller			A
Steven Barbee			Y	Glenn Leach			Y
Lynn Beasley			Y	Mark A. McClanahan			Y
David Belluck			Y	John S. Morawetz			P
Robert Benson			A	Richard W. Niemeier			Y
Kyle Blackman			Y	William Pepelko			N
Jonathan Borak			A	Zarena Post			A
William Bress			A	George Rodgers			Y
Luz Claudio			A	George Rusch, Chair			Y
George Cushmac			Y	Bob Snyder			A
Ernest Falke			N	Thomas J. Sobotka			A
Larry Gephart			Y	Kenneth Still			A
John Hinz			P	Patricia Ann Talcott			A
Jim Holler			Y	Richard Thomas			A
Thomas C. Hornshaw			Y	Thomas Tuccinardi/ Doan Hansen			A
Nancy K. Kim			A	Ben Jackson			A
				TALLY			13/15

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	0.32 ,( )	0.22 ,( )	0.11 ,( )	0.08 ,( )

AEGL 1 Motion: _____ **Second:** _____

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: M. McClanahan **Second:** L. Gephart

Approved by Chair: _____ **DFO:** _____ **Date:** 3/12/98